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Neuroprognostication in the First Six hours

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Abstract:

Early neuroprognostication following cardiac arrest or acute brain injury remains a complex and high-stakes clinical challenge. Accurate prediction of neurological outcomes is limited during the initial hours due to biological instability, confounding factors such as sedation, temperature management, and systemic derangements, and the dynamic evolution of cerebral injury. Multimodal assessment, integrating clinical examination, electrophysiology, biomarkers, brain-directed physiologic monitoring, and early neuroimaging, provides a structured framework to evaluate injury severity and guide acute management. While ultra-early prognostic indicators exist, their reliability is constrained, and premature interpretation risks self-fulfilling errors, particularly through early withdrawal of life-sustaining therapy. This review synthesizes current evidence on early neurological assessment within

the first six hours post-cardiac arrest, highlighting the role of sequential evaluation, confounder management, and multimodal integration. By contextualizing physiological data with imaging, biomarkers, and continuous monitoring, clinicians can optimize acute care, stabilize patients, and defer definitive prognostication until biological signals regain interpretability.

Keywords: Neuroprognostication, Cardiac arrest, Early neurological assessment, Hypoxic-ischemic brain injury

Abbreviations:

Return of spontaneous circulation - ROSC

CA (CA)

withdrawal of life-sustaining therapy (WLST)

Glasgow Coma Scale (GCS)

Electroencephalogram (EEG)

Somatosensory evoked potentials (SSEPs)

continuous electroencephalogram (cEEG)

Targeted temperature management (TTM)

magnetic resonance imaging (MRI)

Computed tomography (CT)

Quantitative EEG (qEEG)

Brainstem auditory evoked potentials (BAEPs)

Visual evoked potentials (VEPs)

Neurofilament light chain (NfL)

Glial fibrillary acidic protein (GFAP)

traumatic spinal cord injury (tSCI)

intracerebral hemorrhage (ICH)

moderate-to-severe traumatic brain injury (msTBI)

Introduction:

CA remains a significant global health challenge, with substantial mortality and a high risk of long-term neurological impairment among survivors. Although advances in emergency care have improved the return of spontaneous circulation (ROSC), a large proportion of patients remain comatose after resuscitation due to hypoxic-ischemic injury to the brain. These comatose patients represent one of the most vulnerable and challenging populations in critical care, given the unpredictability of neurological recovery, their inability to communicate and the need for critical treatment decisions to be made during a period of profound diagnostic uncertainty [13].

Globally, post-cardiac-arrest-coma and acute brain injury account for a significant number of deaths and long-term disabilities. Data analyses indicate that while 24% of out-of-hospital CA (CA) patients reach hospital admission, only 9% survive to discharge, and survivors show a wide range of neurological outcomes. More than 80% of discharged CA survivors are initially comatose, with around 50% remaining comatose after 72 hours, highlighting the severity and unpredictability of brain injury following ROSC. Despite this, the most common cause of death in post-CA patients is not brain injury, but withdrawal of life-sustaining therapy (WLST). This raises a major ethical concern, as the patient may die because of the decision to stop treatment rather than true, proven brain failure. This underlines the influence neuroprognostication has on survival [1].

However, early neurological prognostication after CA is prone to significant uncertainty and may lead to premature WLST in patients who still have the potential for neurological recovery. Recognising the limitations of early assessment and the risk of self-fulfilling prognostic error, this article addresses these challenges by compiling and synthesising current evidence and guideline-based recommendations to support more structured, reliable, and ethically informed decision-making during the early post-CA period.

Methodology:

This literature review was conducted to collate and synthesize current evidence regarding early neuroprognostication after cardiac arrest and acute brain injury, with emphasis on physiological monitoring, biomarkers, neuroimaging, and clinical assessment in the first six hours post-injury.

Search Strategy and Database:

Relevant articles were identified through PubMed, PMC, and Scopus databases using keywords including “cardiac arrest”, “hypoxic-ischemic brain injury”, “early neuroprognostication”, “EEG”, “SSEP”, “biomarkers”, “neuroimaging”, “temperature management”, and “neurological assessment”. Only English-language, peer-reviewed articles with full-text availability were considered.

Screening and Selection:

Abstracts were screened for relevance to early neuroprognostic strategies, physiological monitoring, and outcomes. Full texts were reviewed to include studies that focused on initial post-resuscitation

assessment, multimodal prognostication frameworks, and guideline recommendations. Studies were selected based on methodological rigor, relevance to first-hour assessment, and applicability to clinical decision-making. Discrepancies in article selection were resolved through discussion and consensus among the reviewers.

Principles of Good Prognostication:

Modern neuroprognostication rests on three related principles. Multimodality, Sequentiality and Non-maleficence. Neuroprognostication should be multimodal since no single test reliably captures the spectrum of hypoxic-ischemic injury. Clinical examination, Electroencephalogram (EEG), Somatosensory evoked potentials (SSEPs), biomarkers, and imaging reflect different contributing processes and accurate prediction depends on piecing the available information together. Secondly, prognostication should be sequential and context-dependent. This owes to the instability of the brain during the early post-CA period, where sedation, paralytics, shock, temperature control, and metabolic disturbances may all affect neurological function. Any predictor tested under such conditions risks being influenced and guidelines emphasize eliminating confounders before interpretation. Finally, prognostication must commit to non-maleficence. The risk of a self-fulfilling prophecy due to premature WLST is high, and early impressions are not sufficient to determine patient outcome, irrespective of their extent [1,3,6,13].

The unreliability of neuroprognostication in the early hours, and to refrain from deciding on their basis, is consistently reported across CA, Transient Ischemic Attack, Intracerebral Hemorrhage and other general neurocritical care guidelines [1,6,13]. Neurological function in this early window is biologically unreliable and heavily confounded. Reflexes may appear depressed, EEG may show suppression related to medications or hypothermia, and biomarkers have only begun to rise. Therefore, assessment of prognosis should be delayed, while stabilization and structured neurological assessment should proceed [1,6,13].

However, in clinical practice, there is often pressure to make early decisions. While outcome and prognosis prediction is unsafe and discouraged, several actions are appropriate and necessary such as stabilization of brain physiology by optimizing oxygenation, perfusion, glucose control, temperature, and ventilation. This follows a sequential approach starting with therapeutic intervention and identifying modifiable factors. This is followed by exclusion of reversible causes such as residual sedation, paralytic agents, metabolic derangements, intoxication, seizures, and structural lesions. Neural monitoring with continuous electroencephalogram (cEEG) is essential during this stage for identifying nonconvulsive seizures, status epilepticus and malignant patterns that require urgent treatment. Most seizures at this stage are nonconvulsive or subtle, and cEEG is vital for detecting these otherwise silent events and guiding anti-seizure treatment. This is followed by Baseline Biomarker Sampling as blood-based biomarkers are an important aspect of the neuroprognostic determination later when absolute values and trends can be interpreted over time [1,6,7,8,11].

Clinical Examination in the First 6 Hours

Clinical examination remains the cornerstone for establishing a patient's current neurological state after ROSC. Structured bedside assessment provides essential information regarding level of consciousness, brainstem function, and gross motor responsiveness, and guides early triage and management decisions. Among available tools, the Glasgow Coma Scale (GCS) remains the most widely used standardized instrument for quantifying consciousness. Its simplicity, reproducibility, and independence from advanced technology make it indispensable during initial evaluation. However, while GCS reliably reflects neurological status at the time of assessment, its value in predicting long-term neurological recovery in the immediate post-CA period is limited [3,13,19].

The neurological examination performed within the first hours after acute hypoxic-ischemic brain injury occupies a paradoxical position: it is clinically indispensable yet prognostically unreliable. Neuroprognostication in comatose survivors of CA carries profound consequences, as judgments of poor outcome frequently precipitate WLST. For this reason, contemporary guidelines consistently recommend deferring definitive neurological prognostication until at least 72 hours after ROSC, once biological confounders have been minimized and neurological signals regain interpretability [1,3,6,14]. Early examination findings, irrespective of severity, should therefore not be used in isolation to infer irreversible neurological injury.

In the emergency department and early intensive care setting, there are no clinical examination findings within the first 6 hours that can independently and reliably predict neurological outcome in comatose survivors of out-of-hospital CA. Early awakening itself lacks a uniform definition, with reported time frames extending up to 72 hours post-ROSC, further underscoring the intrinsic uncertainty of assessments performed during this window [1,14]. Prognostic interpretation during this period is particularly vulnerable to misattribution unless conducted in the absence of sedation and other major confounders.

Multiple physiological and treatment-related factors transiently suppress neurological function in the early post-arrest phase without reflecting irreversible injury. Sedative and analgesic agents, neuromuscular blockade, and residual anesthetics may abolish motor responses and brainstem reflexes. Targeted temperature management (TTM) alters neuronal signaling, delays drug metabolism, and suppresses reflex activity, rendering early clinical findings biologically unstable. Systemic disturbances, including hypoxia, hypercapnia, hypotension, dysglycemia, electrolyte imbalance, acid-base derangement, and hepatic or renal dysfunction can independently depress consciousness. Ongoing seizures or nonconvulsive status epilepticus may further impair responsiveness while remaining clinically occult in the absence of EEG monitoring. Intoxication with alcohol or other neuroactive substances may closely mimic severe structural brain injury. For these reasons, guideline recommendations emphasize that prognostic interpretation of the neurological examination should only occur after confounders have been excluded or resolved [1,14]. Importantly, determinants of overall survival such as refractory shock, multiorgan failure, or severe systemic illness must be considered separately and not conflated with neurological prognosis.

Certain clinical signs, including the bilateral absence of pupillary light reflexes, have established prognostic value when assessed at appropriate time points. However, when evaluated within the first 72 hours after ROSC, these findings are associated with higher false-positive rates, substantially limiting their reliability. Premature interpretation of such signs risks misclassification of prognosis, with potentially fatal consequences in the context of WLST decisions. This reinforces timing, not merely the presence or absence of a sign, as a critical determinant of prognostic validity [1,6].

The purpose of the clinical neurological examination in the first 6 hours is therefore frequently misunderstood. Its appropriate role is not definitive outcome prediction, but rather early stratification of injury severity, identification of immediately reversible causes, and guidance of acute management. In practice, however, early neuroprognostication remains highly variable and unsystematic, contributing to premature and unreliable judgments [6]. Consistent with this, most deaths among patients who achieve ROSC occur following WLST based on perceived poor neurological prognosis, often within the first day of admission. Emerging evidence suggests that a substantial proportion of these early decisions may be inappropriate, resulting in preventable mortality among patients who could otherwise achieve meaningful neurological recovery [13].

These observations indicate that the core problem lies not in performing early neurological examinations, but in how their findings are interpreted. A structured, multimodal framework, emphasizing delayed prognostication, serial reassessment, and integration of clinical findings with electrophysiological, biochemical, and imaging data, offers a clear strategy to mitigate bias and reduce self-fulfilling prognostic error [6,14]. In this context, emerging decision-support systems, including artificial intelligence-based models, may further enhance consistency by integrating complex data streams and reinforcing guideline-concordant timing and interpretation. Accordingly, early clinical examination should be deliberately reframed as a foundation for stabilization and escalation of care, with prognostic conclusions deferred until neurological assessment regains biological reliability [6,14].

Neurophysiology Within the First Hours

Neurophysiological assessment provides the earliest objective insight into cerebral function following CA, particularly when clinical examination is obscured by sedation, neuromuscular blockade, or TTM. Among available modalities, EEG is the most widely applied bedside tool for assessing the severity and evolution of hypoxic-ischemic brain injury. EEG reflects real-time cortical activity and enables continuous evaluation of background organization, reactivity, and epileptiform activity, thereby complementing the limitations of early clinical examination [3,19].

In the hyperacute post-arrest period, EEG serves primarily as a physiological monitor rather than a definitive prognostic instrument. Continuous EEG is especially valuable, as seizures are common among comatose survivors of CA and frequently non-convulsive, rendering them clinically silent without electrophysiological monitoring. EEG also facilitates early characterization of injury severity through identification of suppressed backgrounds, burst-suppression patterns, or periodic discharges.

However, interpretation during this phase must remain cautious, as sedative exposure, hypothermia, and evolving cerebral physiology substantially influence EEG appearance [11,19,20].

Highly malignant EEG patterns, including background suppression and burst-suppression, may emerge within the first hours following return of spontaneous circulation and are classically associated with severe hypoxic-ischemic injury. In this ultra-early window, however, the prognostic significance of these patterns remains limited. EEG abnormalities may improve as sedative agents are metabolized and rewarming progresses, and early suppression does not necessarily indicate irreversible injury. Rhythmic or periodic discharges may also appear, reflecting heightened cortical excitability and increased seizure propensity. These patterns often occupy the ictal-interictal continuum and represent dynamic, evolving pathophysiology rather than fixed structural damage, underscoring the necessity of longitudinal assessment rather than static interpretation [11,13,20].

The evolving nature of early EEG abnormalities highlights the importance of continuous rather than intermittent monitoring. Brief EEG recordings have limited sensitivity for detecting non-convulsive status epilepticus and rapidly changing pathological patterns. In contrast, continuous EEG provides sustained surveillance, enabling detection of evolving seizures, assessment of treatment response, and early identification of neurological deterioration. This is particularly relevant in the immediate post-resuscitation period, during which cerebral physiology may change abruptly as compensatory mechanisms fail and secondary injury evolves [11].

Despite its diagnostic utility, early EEG should not be used for definitive neurological prognostication. Although malignant EEG features may appear soon after resuscitation, reliable prognostic interpretation requires exclusion of confounders such as residual sedation, hypothermia, and metabolic derangements. Consistent with broader neuroprognostication principles, neurophysiology literature recommends deferring prognostic conclusions until at least 72 hours after return to normothermia, when EEG findings demonstrate greater biological stability and predictive validity [19,20,21].

Quantitative EEG (qEEG) further augments early neurophysiological assessment by translating complex waveforms into simplified indices of suppression, rhythmicity, and power distribution. These tools facilitate rapid identification of seizures and concerning background patterns, particularly in settings where continuous expert EEG interpretation is not immediately available. During the early post-arrest period, when cerebral activity is highly labile, qEEG may enhance situational awareness and support timely therapeutic intervention, while remaining adjunctive to expert qualitative interpretation [11].

Taken together, early EEG and qEEG provide essential information regarding cerebral activity, seizure burden, and evolving hypoxic-ischemic injury in the immediate post-CA period. Their value lies in physiological monitoring and treatment guidance rather than outcome determination. Accordingly, neurophysiological findings should be integrated within a delayed, multimodal prognostic framework incorporating clinical examination, imaging, biomarkers, and serial reassessment to avoid premature or overly pessimistic conclusions [11,13,19].

Early Neuroimaging

Neuroimaging plays a critical role in the early evaluation of comatose patients following CA by defining structural integrity and excluding alternative causes of coma. Computed tomography (CT) and magnetic resonance imaging (MRI) are the principal modalities employed, each serving distinct purposes within the acute assessment pathway. Non-contrast head CT is typically the first-line study owing to its speed, availability, and ability to rapidly identify immediately life-threatening pathology such as intracranial hemorrhage or large territorial infarction [3,13,19].

In the context of hypoxic–ischemic brain injury, CT findings associated with severe injury include loss of grey-white matter differentiation and sulcal effacement, reflecting diffuse cerebral edema. Quantitative measures such as the grey-white matter ratio have been explored as prognostic indices, with specific thresholds selected to maximize specificity for poor outcome. However, within the first 6 hours after return of spontaneous circulation, CT demonstrates poor sensitivity for hypoxic-ischemic injury, and a normal early scan does not exclude severe neurological damage. Consequently, early CT findings should not be used in isolation to infer neurological prognosis [1,6,13].

MRI provides superior sensitivity for detecting early ischemic injury due to its higher soft-tissue resolution, particularly through diffusion-weighted imaging and apparent diffusion coefficient mapping. Despite this advantage, MRI is rarely feasible in the hyperacute post-arrest period because of patient instability, logistical constraints, and the need for ongoing critical care support. Even when obtained early, diffusion abnormalities may underestimate the eventual extent of injury, as ischemic changes evolve over time. Functional MRI and other advanced techniques offer insights into network integrity and residual function, but their role in the immediate post-resuscitation period remains investigational and adjunctive rather than prognostic [3,13,19].

Accordingly, the primary role of neuroimaging within the first 6 hours is diagnostic rather than prognostic. Early CT and, when feasible, MRI are essential for identifying intracranial hemorrhage, large ischemic syndromes, or other structural lesions that may explain the clinical presentation and require urgent intervention. Prognostic interpretation of neuroimaging findings should be deferred and integrated with serial assessments and complementary modalities once biological reliability is restored [1,3,6,13].

Temperature Management and Its Impact on Prognosis

Targeted temperature management (TTM) remains a central component of post-CA care due to its role in mitigating secondary hypoxic-ischemic brain injury. Reductions in core temperature lower cerebral metabolic demand, attenuate excitotoxic neurotransmitter release, suppress inflammatory cascades, and preserve blood-brain barrier integrity during reperfusion. Experimental and clinical data demonstrate that even modest temperature reductions substantially decrease cerebral oxygen consumption, thereby increasing neuronal tolerance to ischemic stress and supporting early neuroprotection [15,17]. These physiological effects formed the rationale for the early adoption of hypothermia protocols in post-CA care.

Subsequent randomized trials, including TTM and TTM2, refined this approach by demonstrating that strict temperature control and prevention of hyperthermia are more critical determinants of outcome than deep hypothermia itself. The absence of a clear neurological advantage for cooling to 33 °C compared with controlled normothermia shifted clinical emphasis toward consistent temperature management, fever avoidance, and controlled rewarming rather than aggressive hypothermia targets [11,14,15]. Importantly, while temperature management confers neuroprotective benefit, it also substantially complicates early neurological assessment. Sedation, neuromuscular blockade, and anti-shivering measures suppress clinical reflexes, while hypothermia itself reduces EEG amplitude, frequency, and reactivity. Consequently, neurological findings obtained during active temperature modulation must be interpreted within their physiological context and should not be used in isolation for prognostication [11,14]. This reinforces the principle that no single modality can reliably predict neurological outcome in the early post-arrest period.

Somatosensory Evoked Potentials

Somatosensory evoked potentials (SSEPs) are among the most robust and reproducible tools in post-CA neuroprognostication and constitute a core element of contemporary multimodal frameworks. SSEPs assess the functional integrity of the thalamocortical sensory pathways by measuring the short-latency cortical N20 response following median nerve stimulation. Preservation of bilateral N20 responses indicates intact thalamocortical connectivity and is associated with the potential for meaningful neurological recovery. Conversely, bilateral absence of the N20 response reflects extensive cortical or subcortical injury and is strongly associated with poor neurological outcome and high mortality [9,12,20].

Within the first six hours after CA, however, the role of SSEPs is limited to early physiological characterization rather than definitive outcome prediction. Early assessments may help establish baseline pathway integrity and contribute to injury stratification, but results must be interpreted cautiously in the presence of confounders. Sedative agents, metabolic derangements, and particularly temperature modulation influence evoked potential latency and amplitude. Hypothermia prolongs SSEP latencies and, at lower temperatures, may abolish the N20 response entirely, rendering ultra-early findings biologically unreliable [1,12,20]. For this reason, guideline recommendations emphasize that SSEP-based prognostication should only be performed after confounders have been excluded and neurological signals have stabilized, typically no earlier than 72 hours after return of spontaneous circulation, particularly in patients treated with TTM [1,12,19].

When applied at appropriate time points and within a multimodal framework, the bilateral absence of the N20 response remains one of the most specific predictors of poor neurological outcome. Its strength lies in its relative resistance to sedative confounding and its direct interrogation of thalamocortical pathway integrity. Nevertheless, even this highly specific marker should not be used in isolation or prematurely to support irreversible decisions.

Other Evoked Potentials

Beyond SSEPs, additional evoked potential modalities offer complementary information but play a more limited role in routine clinical practice. Brainstem auditory evoked potentials (BAEPs) assess the integrity of the auditory pathways traversing the lower brainstem. Bilateral absence of central BAEP waves reflects severe pontine or midbrain dysfunction and is associated with an unfavorable neurological outcome, offering high specificity but limited sensitivity [12]. As such, BAEP abnormalities strongly suggest severe injury when present but cannot reliably exclude poor outcome when normal.

Visual evoked potentials (VEPs) interrogate the integrity of the visual pathways and occipital cortex but are limited by technical variability, susceptibility to sedation, and inconsistent reproducibility. Event-related potentials such as P300 and mismatch negativity provide insights into higher-order cortical processing but remain largely investigational in the post-CA population [12,19]. Collectively, evoked potentials sample neurological function across multiple levels of the neuraxis, from brainstem to cortex. Among these, SSEPs remain the most clinically impactful due to their reproducibility, physiological specificity, and validated prognostic performance within multimodal frameworks.

Blood-Based Biomarkers in the First 6 Hours

Blood-based biomarkers provide biologically grounded insight into neuronal and axonal injury and play a supportive role in early neuroprognostication, particularly when clinical examination and neurophysiology are confounded [3,6,7]. Their principal value in the first six hours lies in establishing an early biological baseline rather than delivering definitive prognostic information. Interpretation relies on understanding the temporal kinetics of injury-related protein release, which often lags behind the initial ischemic insult [6,7,14].

Neurofilament light chain (NfL), a cytoskeletal protein localized predominantly to large myelinated axons, is a sensitive marker of axonal injury. Following hypoxic-ischemic brain injury, axonal degeneration evolves gradually, resulting in delayed NfL release into cerebrospinal fluid and systemic circulation. Numerous observational studies and meta-analyses demonstrate strong associations between elevated NfL concentrations and poor neurological outcome after CA, with excellent discriminatory performance at later time points [8,18]. However, within the first six hours, NfL levels exhibit substantial overlap between favorable and unfavorable outcome groups, reflecting incomplete axonal disintegration. Consequently, early NfL elevations should be interpreted as indicators of injury burden rather than definitive predictors, and current evidence does not support their use for ultra-early withdrawal-of-care decisions [8,18].

Other biomarkers reflect distinct components of hypoxic–ischemic injury and exhibit heterogeneous temporal profiles. Glial fibrillary acidic protein (GFAP), released following astroglial injury and blood-brain barrier disruption, may rise earlier than axonal markers, but reported thresholds vary widely and prognostic associations are inconsistent, particularly in the ultra-early phase. Ubiquitin carboxy-

terminal hydrolase L1 (UCH-L1), a neuronal cytoplasmic protein, demonstrates relatively rapid release but lacks validated early cut-off values and remains insufficiently characterized in post-CA populations [7]. Neuron-specific enolase (NSE), while endorsed by international guidelines, demonstrates delayed peak concentrations and reduced specificity when measured early, rendering it unsuitable for prognostication within the first 24 hours [1,3,13].

Taken together, blood-based biomarkers offer valuable mechanistic insight into hypoxic–ischemic brain injury but have limited standalone prognostic utility within the first six hours after CA. NfL provides the strongest overall prognostic signal but reflects delayed axonal injury, while GFAP and UCH-L1 lack standardized thresholds and robust early validation. Accordingly, early biomarker measurements should be regarded as supportive and hypothesis-generating rather than determinative, reinforcing the necessity of delayed, multimodal prognostication strategies to minimize self-fulfilling prognostic error and premature withdrawal of life-sustaining therapy [7,13].

Neurophysiology Within the First Hours

Neurophysiological tests, particularly EEG and evoked potentials , are valuable non-invasive bedside tools for early neurological assessment. EEG records cerebral electrical activity via multiple scalp electrodes and remains the most widely used modality for assessing the severity of hypoxic-ischemic brain injury. EEG patterns reflect real-time cerebral function, and certain findings, commonly termed “highly malignant” patterns, such as background suppression or burst-suppression, are associated with severe brain injury. EEG is also useful for characterizing the patient’s current neurological state when clinical examination is limited [3,19].

In the early hours following CA, neurophysiological assessment relies predominantly on EEG, as clinical examination is frequently confounded by sedation, neuromuscular blockade, and targeted temperature management. cEEG monitoring is particularly valuable, as seizures are common in comatose post-CA patients and are often non-convulsive, rendering them undetectable without electrical monitoring. EEG also aids in characterizing injury severity through findings such as background suppression, burst-suppression, and periodic discharges; however, these features must be interpreted cautiously in the presence of sedation and hypothermia [11,19,20].

Within the ultra-early post-arrest period, EEG may demonstrate highly malignant patterns that are typically associated with severe hypoxic-ischemic injury. However, the prognostic significance of these findings is limited at this stage, as EEG abnormalities may evolve with sedative clearance and rewarming. Rhythmic and periodic discharges may also appear early, reflecting increased cortical excitability and an elevated risk of seizures. These patterns exist along the ictal-interictal continuum and often represent dynamic, evolving injury rather than fixed irreversible damage, underscoring the importance of longitudinal assessment [11,13,20].

This evolving nature highlights the distinction between intermittent and cEEG monitoring. Short recordings of 20-40 minutes have limited sensitivity for detecting non-convulsive status epilepticus and rapidly changing pathological patterns, whereas continuous EEG allows sustained surveillance,

enabling detection of evolving seizures, assessment of treatment response, and identification of neurological deterioration as it occurs. Given that logistical constraints often delay EEG initiation in early intensive care settings, continuous monitoring is especially valuable during the first hours after resuscitation, when cerebral physiology may change abruptly [11].

Despite its diagnostic utility, early EEG should not be used for definitive prognostication. Although malignant EEG features may appear soon after ROSC, reliable prognostic interpretation requires exclusion of confounders such as residual sedation, hypothermia, and metabolic derangements. Accordingly, neurophysiology guidelines recommend delaying definitive prognostication until at least 72 hours after return to normothermia, as early EEG abnormalities are suggestive but not determinative of long-term outcome [19,20,21].

qEEG augments early neurophysiological assessment by transforming complex waveforms into simplified metrics, including suppression indices, rhythmicity measures, and power ratios. These displays facilitate rapid recognition of seizures, background suppression, and concerning periodic patterns, even among clinicians without advanced EEG expertise. qEEG is particularly valuable during the early post-arrest period, when cerebral activity may fluctuate rapidly and continuous expert interpretation may not be immediately available [11].

Taken together, early EEG and qEEG provide critical insight into cerebral activity, seizure burden, and evolving hypoxic-ischemic injury in the immediate post-CA period. However, findings must be interpreted within a delayed, multimodal prognostic framework that integrates clinical examination, imaging, biomarkers, and serial assessments to avoid premature or overly pessimistic conclusions [11,13,19].

Brain-Directed Physiologic Monitoring

Brain-directed physiological monitoring offers additional insight into evolving cerebral dysfunction after CA. Cerebral oximetry using near-infrared spectroscopy enables continuous, non-invasive assessment of regional cerebral oxygenation. While absolute values may not directly reflect neuronal viability, longitudinal trends can reveal imbalances between cerebral perfusion and metabolism during the early post-arrest period [17].

Invasive neuromonitoring strategies, such as intracranial pressure and cerebral perfusion pressure monitoring, are well established in traumatic brain injury and intracerebral hemorrhage but are not routinely used after CA. Although the underlying physiological principles remain relevant, these interventions are invasive and may introduce additional injury in a globally ischemic brain. Conceptual application of brain-directed monitoring principles supports a systems-level approach integrating hemodynamic optimization, temperature control, and delayed multimodal prognostication [11,16,17].

Early Neuroimaging

Neuroimaging provides essential information regarding structural brain integrity following CA or acute brain injury. CT and MRI are the principal modalities used, with CT typically serving as the first-line investigation due to its rapid acquisition and widespread availability. CT enables prompt exclusion of alternative causes of coma, such as intracranial hemorrhage. On CT imaging, the gray-white matter ratio is commonly used as a prognostic marker, with specific thresholds selected to maximize specificity for poor outcome. While CT is optimal for early triage and exclusion of surgical emergencies, MRI offers superior sensitivity for detecting early ischemic injury due to its higher soft tissue resolution [3,13,19].

Early neuroimaging plays an important role in the initial assessment of comatose patients; however, its prognostic value within the first 6 hours after ROSC is limited and must be interpreted cautiously. Non-contrast head CT is frequently obtained early because it is rapidly available and can identify immediately life-threatening pathology. Early radiographic signs of severe hypoxic-ischemic injury include loss of gray-white matter differentiation and sulcal effacement, reflecting diffuse cerebral edema. Nonetheless, CT has poor sensitivity for hypoxic-ischemic injury in the hyperacute phase, and a normal scan does not exclude severe neurological damage.

MRI is rarely feasible in the first hours following CA due to patient instability and logistical constraints. Even when performed early, diffusion-weighted imaging may underestimate the extent of ischemic injury, as diffusion abnormalities evolve over time. Consequently, early MRI findings should not be used in isolation for neurological prognostication. Despite these limitations, early neuroimaging remains essential for identifying alternative or concurrent causes of coma, including intracranial hemorrhage, large territorial infarction, or other structural lesions requiring urgent intervention [1,3,6,13].

The Risk of Misinterpretation

Accurate neuroprognostication is challenged by multiple sources of uncertainty, particularly when relying on time-dependent physiological and blood-based markers. Prognostication after acute brain injury is inherently complex, and clinicians must recognize the limitations of available predictors. The primary objective is to provide timely, accurate prognostic information that aligns treatment decisions with patient values while avoiding premature conclusions [6].

Sampling Timing Errors

The timing of prognostic assessment is critical, as premature evaluation may lead to inappropriate WLST in patients who might otherwise achieve meaningful neurological recovery. Current guidelines emphasize delaying neurological prognostication in comatose survivors of CA. In patients not treated with therapeutic hypothermia, assessment should be deferred for a minimum of 72 hours after ROSC. In those treated with hypothermia, prognostication should occur no earlier than 72 hours after rewarming [1].

Blood-based biomarkers exhibit disease-specific temporal release profiles, requiring careful selection of sampling time points to avoid misinterpretation. For example, GFAP peaks within 2-6 hours in intracerebral hemorrhage but may peak 2-3 days after subarachnoid hemorrhage. Although guidelines recommend measuring NSE between 24 and 72 hours after CA, reliance on external laboratories can delay result availability, limiting its practical utility as a timely prognostic marker [7].

Hemolysis and Biomarker Interpretation

NSE is particularly vulnerable to pre-analytical errors, most notably hemolysis. While NSE is predominantly neuronal, it is also present in erythrocytes and platelets. Hemolysis leads to the release of NSE from these non-neuronal sources, resulting in falsely elevated serum levels and potentially overly pessimistic prognostic interpretations. Consequently, hemolyzed samples substantially compromise the validity of NSE measurements [7,8].

In contrast, emerging biomarkers such as NfL may offer advantages, including improved specificity for neuroaxonal injury and earlier applicability in neuroprognostication. NfL remains under active investigation but represents a promising alternative to traditional markers [18].

Hemodynamic Parameters and Systemic Ischemia

Systemic hemodynamic parameters reflect the severity of global ischemia following CA but lack sufficient specificity to function as independent predictors of neurological outcome. Mean arterial pressure, serum lactate, and shock indices provide insight into perfusion adequacy and metabolic stress during and after resuscitation. Persistent hypotension and elevated lactate levels are associated with ongoing tissue hypoxia and increased risk of secondary organ injury, including cerebral injury [16,17].

Following ROSC, cerebral blood flow undergoes dynamic transitions from early hyperemia to subsequent hypoperfusion and delayed recovery. During this vulnerable period, cerebral autoregulation is frequently impaired, rendering cerebral perfusion sensitive to systemic blood pressure fluctuations. Observational studies suggest that maintaining higher mean arterial pressures early after resuscitation may support cerebral perfusion and correlate with improved neurological outcomes when autoregulatory mechanisms are compromised. However, these measures should be interpreted as contextual indicators of physiological stress rather than definitive predictors of long-term neurological recovery [17].

Special Populations

Traumatic Brain Injury

Neuroprognostication in moderate-to-severe traumatic brain injury (msTBI) is particularly challenging due to substantial pathophysiological heterogeneity. Current guidelines advise against using individual variables, such as GCS scores, age, or CT-based scoring systems, in isolation to predict outcome. Bilateral pupillary non-reactivity on admission is considered the only moderately reliable early clinical predictor of six-month functional outcome when assessed without confounding factors [4].

Validated prognostic models, including the CRASH and IMPACT models, provide moderately reliable estimates of six-month mortality and functional outcome. A critical distinction between msTBI and hypoxic-ischemic injury lies in mortality timing: approximately 80% of deaths in msTBI occur in the ICU following WLST, with more than half occurring within the first 72 hours. This highlights the heightened risk of premature prognostication in TBI compared with the delayed observation periods typically required for hypoxic-ischemic brain injury [4].

Intracerebral Hemorrhage

Accurate prognostication in intracerebral hemorrhage (ICH) is complicated by the risk of self-fulfilling prophecy. While hematoma volume and location are important determinants of injury severity, no single clinical variable or grading system reliably predicts outcome in isolation. The original ICH score is useful for clinical communication but should not independently guide decisions regarding limitation of life-sustaining therapy. Guidelines recommend deferring formal prognostication for at least 48-72 hours after admission [5].

Spinal Cord Injury

Prognostication in traumatic spinal cord injury (tSCI) focuses on functional independence and ambulation at one year. Guidelines caution that individual variables, including age or associated injuries, are unreliable predictors of outcome. The most reliable predictors of neurological recovery include MRI findings and the initial neurological level of injury. The Dutch Clinical Prediction Rule is considered a moderately reliable tool for predicting one-year ambulation [10].

Pediatric CA

In pediatric CA, neuroprognostication prioritizes injury stratification to identify candidates for neuroprotective interventions. EEG remains a standard tool for seizure detection and background assessment. While certain EEG patterns correlate with injury severity, the impact of aggressive seizure suppression on long-term outcomes is still under investigation. Biomarkers such as NfL, NSE, and GFAP assist in injury stratification, though their temporal dynamics differ from adults, with GFAP and NSE often peaking days to weeks after ROSC. Among available biomarkers, NfL currently demonstrates the strongest predictive value for unfavorable outcomes [21].

Multimodal Early Assessment

Early assessment in the first hours following CA or acute brain injury is focused on stabilization, data acquisition, and confounder elimination rather than definitive prognostication. The multimodal approach begins immediately but must be interpreted within strict temporal constraints. The 0-6-hour window serves as a foundational screening phase that informs later, more accurate prognostic assessment. Early data collection, when unconfounded, feeds into definitive multimodal evaluation at

≥72 hours, at which point decisions regarding WLST should be considered in alignment with patient values and preferences [1,3,6,7].

Clinical Decision-Making and Outcomes

Early clinical findings strongly influence treatment decisions following CA, particularly within the first hours after ROSC. Neurological examination, early imaging, and physiological parameters frequently guide decisions regarding escalation of neuroprotective therapies. However, substantial evidence demonstrates that neurological prognostication performed too early is unreliable. Suppressed neurological responses during this period may reflect sedation, hypothermia, or transient cerebral dysfunction rather than irreversible injury. Early WLST, often occurring within 24-72 hours, accounts for a large proportion of post-CA deaths and may result in preventable mortality among patients with potential for meaningful recovery [13].

Accordingly, early data should guide supportive and neuroprotective care rather than definitive prognostic conclusions. Multimodal assessment performed at appropriate time points improves prognostic accuracy and reduces false pessimism. Delaying definitive prognostication until confounding factors resolve, typically at least 72 hours after injury or rewarming, aligns clinical decision-making with the biological reality of delayed and non-linear neurological recovery [6].

Family communication is central during periods of prognostic uncertainty. Clinicians must convey uncertainty transparently, avoid absolute predictions, and engage in shared decision-making that respects patient values. Time-limited trials of ongoing intensive care are recommended when prognosis remains indeterminate, allowing observation of neurological trends while maintaining alignment with patient preferences [3,6].

Premature WLST carries ethical implications related to nihilism bias and self-fulfilling prophecy. Early limitation of therapy guarantees death and precludes the possibility of recovery, reinforcing inaccurate prognostic beliefs. Contemporary guidelines emphasize standardized prognostic pathways, delayed assessment, and cautious interpretation of early findings to mitigate these risks and safeguard patient autonomy [1].

Future Directions

Future advances in neuroprognostication are expected to arise from integrated, multimodal strategies rather than reliance on isolated tests. Next-generation biomarkers, particularly early trajectories of NfL and GFAP, capture complementary aspects of neuronal and astroglial injury and may offer prognostic insight before traditional modalities become reliable. Multi-analyte biomarker panels may further enhance discriminative accuracy by accounting for biological heterogeneity and reducing dependence on fixed thresholds [18,19,20].

Advances in neurophysiology are likely to be driven by artificial intelligence-based EEG analysis. Automated pattern recognition and machine-learning techniques may identify subtle temporal and spatial features beyond visual interpretation, reduce inter-observer variability, and enable broader

clinical implementation. Integration of EEG-derived features with physiological data streams may support dynamic reassessment of injury severity rather than static, time-point predictions [7,11].

Imaging advances, including high-resolution diffusion-weighted MRI and CT perfusion, may further refine early detection of ischemic injury and microvascular dysfunction. When integrated with biomarker trajectories and advanced EEG analytics, early imaging may contribute to individualized, continuously updated prognostic frameworks [7,8,18].

Limitations:

Despite extensive literature, several limitations constrain the current understanding of ultra-early neuroprognostication. The evidence base is heterogeneous, encompassing variable study designs, patient populations, timing of assessment, and outcome measures. Many studies are observational with small sample sizes, limiting generalizability. Confounding factors such as sedation, temperature modulation, metabolic derangements, and variable timing of EEG or biomarker measurement introduce significant bias. Data on pediatric populations, traumatic brain injury, and rare pathologies are limited, further restricting applicability. Additionally, while multimodal frameworks are widely recommended, integration of physiological, imaging, and biochemical data varies across centers, highlighting gaps in standardized protocols. Finally, the influence of early clinical decision-making on outcomes, particularly via withdrawal of life-sustaining therapy, may introduce self-fulfilling biases that distort prognostic accuracy.

Conclusion:

Early neuroprognostication in comatose patients following cardiac arrest or acute brain injury is constrained by biological instability, confounding factors, and the dynamic evolution of cerebral injury. Definitive prediction of long-term neurological outcome within the first six hours is unreliable, and premature interpretation carries significant ethical and clinical risks, particularly regarding withdrawal of life-sustaining therapy. A multimodal, sequential approach, integrating clinical examination, continuous electrophysiological monitoring, biomarkers, brain-directed physiologic assessment, and early neuroimaging, supports stabilization, injury stratification, and identification of reversible causes without prematurely determining prognosis.

Guideline-concordant deferral of definitive prognostic decisions until confounders are minimized and biological signals regain reliability maximizes patient safety and aligns clinical care with evolving neurological recovery. Future advances will likely arise from integration of real-time monitoring, AI-assisted EEG analytics, advanced biomarkers, and high-resolution imaging to refine early assessment, enhance prognostic accuracy, and guide individualized, evidence-based decision-making.

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