Concise Definitive Review

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Prognosis in Severe Brain Injury

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Background: The prediction of neurologic outcome is a fundamental concern in the resuscitation of patients with severe brain injury.
Objective: To provide an evidence-based update on neurologic prognosis following traumatic brain injury and hypoxic-ischemic encephalopathy after cardiac arrest.
Data Source: Search of the PubMed database and manual review of bibliographies from selected articles to identify original data relating to prognostic methods and outcome prediction models in patients with neurologic trauma or hypoxic-ischemic encephalopathy.
Data Synthesis and Conclusion: Articles were scrutinized regarding study design, population evaluated, interventions, outcomes, and limitations. Outcome prediction in severe brain injury is reliant on features of the neurologic examination, anatomical and physiological changes identified with CT and MRI, abnormalities detected with electroencephalography and evoked potentials, and physiological and biochemical derangements at both the brain and systemic levels. Use of such information in univariable association studies generally lacks specificity in classifying neurologic outcome. Furthermore, the accuracy of established prognostic classifiers may be affected by the introduction of outcome-modifying interventions, such as therapeutic hypothermia following cardiac arrest. Although greater specificity may be achieved with scoring systems derived from multivariable models, they generally fail to predict outcome with sufficient accuracy to be meaningful at the single patient level. Discriminative models which integrate knowledge of genetic determinants and biologic processes governing both injury and repair and account for the effects of resuscitative and rehabilitative care are needed. (*Crit Care Med* 2013; 41:1104–1123)
Key Words: cardiac arrest; coma; Corticosteroid Randomization After Significant Head Injury; hypoxic-ischemic encephalopathy; International Mission on Prognosis and Analysis of Clinical Trials in Traumatic Brain Injury; prognosis; traumatic brain injury

BURDEN OF SEVERE BRAIN INJURY

The resuscitation of patients with severe brain injury (SBI), which we define as an insult severe enough to cause an acute and persistent loss of consciousness and to entail a significant likelihood of death or of long-term disability, is a central concern in intensive care medicine. Although the etiologies of SBI are diverse, the most prevalent causes are traumatic brain injury (TBI) and cardiac arrest (CA). Severe TBI is the leading cause of death during the first five decades of life, with more than 50,000 deaths annually and functional disability in more than 40% of survivors in the United States (1). The prevalence of CA is estimated at half a million cases per year in the United States with less than 30% of patients surviving until hospital discharge and high rates of disability in survivors despite advances in cardiopulmonary resuscitation and post-CA care (2–5).

The introduction of therapeutic hypothermia for comatose survivors after CA has improved not only survival but also the functional status of survivors (4–7). Randomized trials have found that up to 50% of comatose CA patients treated with hypothermia may have a good 1-year neurologic outcome (4, 5, 8). With declining mortality, there is a pressing need to accurately and reliably predict the likelihood of functional recovery, yet existing prognostic models have many limitations. They do not recognize potentially critical determinants of outcome, such as genetic susceptibility, biological heterogeneity, and the effects of incremental refinements in intensive care and rehabilitation. Current prognostic models in SBI generally estimate the probability of a dichotomous endpoint, usually an unfavorable outcome defined as death or severe disability; however, there is intrinsic interest in understanding the likelihood of a favorable outcome, or in being able to discriminate individual probabilities in a range of outcomes, not just binary favorable/

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unfavorable ones. Finally, the unfounded assumption of an unfavorable prognosis may become "self-fulfilling" if life-sustaining treatment is withheld on the basis of that belief (9). An ideal prognostic system would help clinicians align realistic estimates of recovery with the mobilization of therapeutic resources at the individual level, thus defeating self-fulfilling prophecies. Consideration of these factors is likely to increase the relevance and accuracy of prognostic algorithms in SBI.

RECOVERY FOLLOWING SBI

The clinical trajectory following SBI can be considered in terms of three basic processes: 1) the emergence of conscious awareness, 2) the recovery of higher neuropsychological processing, and 3) the return of functional capacity (10). States commonly seen following coma are the vegetative state (VS) (11, 12), the minimally conscious state (MCS) (13), and emergence from minimally conscious state (EMCS), marked by reliable functional communication and functional object use after MCS (14); further stages of recovery are characterized by the restoration of higher cognitive functions, such as attention, memory, and executive functions (**Fig. 1**). The time course of recovery is variable; in a subset of patients, phenotypic characteristics may remain fixed ("plateau"), resulting in states of chronically impaired consciousness.

In contrast to coma, patients in a VS demonstrate signs of arousal; however, they are incapable of self or contextual awareness (15). The pattern of brain damage can be substantially different in VS patients depending on the etiology. A common neuropathologic finding after CA is diffuse or multifocal cortical ischemia, often associated with lesions in the thalamus and basal ganglia injury (16), with relative sparing of the brainstem (17). In TBI, the most frequent pattern is traumatic axonal injury with lesions clustering in the corpus callosum and brainstem (18). Clinical descriptors of VS may not accurately identify underlying conscious processes; with the help of functional neuroimaging or high-density electroencephalography (EEG), it has been demonstrated that a subset of patients who meet criteria for VS have patterns of cortical activation that are analogous to those of conscious controls (19, 20). MCS is also generally seen in patients with extensive hemispheric damage, although cortico-cortical and corticothalamic connectivity may be better preserved in MCS than in VS (21–23). In contrast to VS, patients with MCS present with unequivocal signs of self or environmental awareness; however, these behaviors are not demonstrated in a reliable fashion (13).

The natural history of patients who are in VS and MCS is not well studied. In a retrospective analysis, 50% of MCS patients and only 3% of VS patients had no or moderate disabilities when evaluated 1 year after injury, and improvement was more rapid and pronounced in the patients who had a traumatic etiology (24). The appearance of visual pursuit may precede recovery of more distinct signs of consciousness (25), and an association has been observed between preserved visual pursuit and the likelihood of functional recovery (26, 27). The time course of recovery may be prognostically significant. In a multicenter study of VS and MCS patients admitted to rehabilitation centers, prediction of functional outcome correlated with the rate of improvement measured with repeated administration of the Disability Rating Scale over the first 2 weeks of observation (28). After recovery of awareness, patients recovering from SBI may have significant neurological impairments, including motor deficits, myoclonus, dystonia, movement disorders, aphasia, neglect, and abulia (29–32). In addition, many survivors of SBI have impairments in attention, memory, executive control, mood disorders,

	Brain death	Coma	Vegetative state	Minimally conscious state	Emergence from minimally conscious state
Eye opening	none	none	occasional	Occasional but inconsistent	present
Visual fixation or pursuit	none	none	none	Occasional but inconsistent	present
Spontaneous movement	none	none	nonpurposeful	present	purposeful
Response to noxious stimuli	none	none, flexion or extension	variable	variable	variable
Verbalization	none	none	none	Occasional but inconsistent	present
Functional communication	none	none	none	Occasional but inconsistent	consistent

Figure 1. Recovery phenotypes following severe brain injury.

TABLE 1. Prognostic Variables Included in the International Mission on Prognosis and Analysis of Clinical Trials and Adapted Corticoid Randomization After Significant Head Injury Models

International Mission on Prognosis and Analysis of Clinical Trials		
Basic Model	**Core Model**	**Lab Model**
Age	Age	Age
GCS	GCS	GCS
Motor score	Motor score	
Pupillary reactivity	Pupillary reactivity	Pupillary reactivity
	Marshall CT classification	Marshall CT classification
	Epidural hematoma	Epidural hematoma
	Traumatic subarachnoid hemorrhage	Traumatic subarachnoid hemorrhage
	Hypoxia	Hypoxia
	Hypotension	Hypotension
		Blood glucose level
		Hemoglobin level
Corticoid Randomization After Significant Head Injury		
Basic Model	**Extended Model**	
Age	Age	
GCS	GCS	
Motor score	Motor score	
Pupillary reactivity	Pupillary reactivity	
Major extracranial injury	Major extracranial injury	
	Marshall CT classification	
	Traumatic subarachnoid hemorrhage	

GCS = Glasgow Coma Scale.
Adapted from Roozenbeek et al (36).

and seizure disorders that have a dramatic impact on the level of functional independence and quality of life (33).

PROGNOSIS IN TBI

Two prognostic scoring systems for TBI have been developed from the analysis of large patient datasets: the International Mission on Prognosis and Analysis of Clinical trials in Traumatic Brain Injury database (IMPACT) and the Corticosteroid Randomization After Significant Head injury trial data (CRASH) (34, 35). IMPACT and CRASH are based on multiple logistic regression models of variables predicting functional outcome at 6 months (**Table 1**). Independently predictive variables cluster around clinical signs (e.g., pupil reactivity and motor responses), neuroanatomic descriptors from cranial CT (midline shift and encroachment of basilar cisterns), and selected physiologic and biochemical derangements (Table 1). Both models discriminate outcomes with areas under the receiver operating characteristic curve (AUC) of 0.6–0.8 and have been calibrated internally and externally (35, 36) (**Table 2**). The external validity of IMPACT and CRASH models was confirmed in an analysis of five more recent studies totaling 9,036 patients, an analysis which did not demonstrate any meaningful difference in prognostic performance between models (36).

Although extensively validated in large datasets, the CRASH and IMPACT scoring systems do not have the accuracy to be meaningful for decision making at the individual patient level. Prognostic estimates always represent probabilities and not absolute certainties on the actual outcome at any given time. The value of IMPACT and CRASH is more apparent in the design and analysis of clinical trials, where they can be used to stratify patients into a priori prognostic categories, and in clinical audits, where they can be used to adjust for case mix.

Genetic Factors

Research suggests that the APOE ε4 allele, which has been linked to Alzheimier's disease, may significantly influence outcome

TABLE 2. Validation of the International Mission on Prognosis and Analysis of Clinical Trials and Adapted Corticoid Randomization After Significant Head Injury Models

Reference/ Country	Study Design	Patients	Definition of Poor Outcome	Prediction of Poor Outcome
Steyerberg et al (34)/ The Netherlands	Data from eight randomized controlled trials and three observational studies	8,509 patients with moderate and severe TBI	GOS 1–3 and death at 6 mo	AUC 0.66–0.84 for core model AUC increased by approximately 0.05 with extended model External validation on 6681 patients with AUC 0.78–0.80
Perel et al (35)/United Kingdom	Prospective multicenter randomized trial	10,008 patients	GOS 1–3 at 6 mo and death at 14 d	Basic model: AUC 0.86 for death and 0.81 for GOS 1–3 Extended model: AUC 0.88 for death and 0.83 for GOS 1–3 External validation on 8509 patients with 0.77 for both models
Roozenbeek et al (36)/ The Netherlands	Data from three randomized controlled trials and two observational studies	9,036 patients from five different large datasets	GOS 1–3 and death at 6 mo	External validation of IMPACT against all five datasets showed good discrimination for death (AUC 0.65–0.83) and GOS 1–3 (AUC 0.66–0.76) External validation of CRASH against all five datasets showed good discrimination for death (AUC 0.66–0.85) and GOS 1–3 (AUC 0.68–0.78)

IMPACT = International Mission on Prognosis and Analysis of Clinical Trials; CRASH = Corticoid Randomization After Significant Head injury; TBI = traumatic brain injury; AUC = area under the curve; GOS = Glasgow Outcome Scale.

following TBI (37–50). Distinct neuropathological features, including amyloid deposits, have been found in patients with the APOE ε4 allele who die of TBI (51). Prospective evaluations demonstrate that TBI patients with the APOE ε4 allele are twice as likely to have an unfavorable outcome compared with those without the allele (37, 38). TBI patients with the ε4 allele have larger parenchymal hematomas (41) and are more likely to remain in prolonged coma (39) and to have posttraumatic seizures (42) and adverse rehabilitation outcome (39, 43). Available data indicate that APOE ε4 is a robust predictor of impaired neuropsychological function and of dementia following TBI (44, 45, 47, 48). Other genes have been linked with outcome after TBI, such as APOE promoter (52), genes encoding for the catechol-o-methyltransferase (53), the dopamine D2 receptor (DRD2) (54), interleukin genes (55), the p53 gene that regulates cell cycle (56, 57), PARP-1 (58), and CACNA1A genes (59). While these observations have generated important hypotheses regarding the biology of TBI and its outcome, broader efforts are needed to capture genome-wide expression patterns in large populations of TBI patients.

Clinical Assessment

Clinical estimation of injury severity has long been the cornerstone outcome prediction after TBI (60) and typically centers on an evaluation of level of consciousness and of brainstem responses (61). The Glasgow Coma Scale (GCS) has been widely adopted as a simple method to numerically express the clinically observed features of consciousness (62). The GCS has several limitations: it does not directly assess brainstem responses, and the value of the verbal and eye subscores is diminished in intubated, aphasic, or aphonic patients and in those who have facial or ocular injury impeding eye evaluation. On the other hand, the GCS motor subscore has robust prognostic value in both CRASH and IMPACT models. Extensor or absent motor responses are associated with poor 6-month functional outcome (35, 63). The more recent Full Outline of UnResponsiveness (FOUR) attempts to address some of the limitations of the GCS by removing any verbal assessment and integrating brainstem responses and breathing patterns (64) (**Fig. 2**). In a recent prospective evaluation of 51 patients with TBI, the AUC of the FOUR score in predicting poor functional outcome (dead, vegetative, or severely disabled) at 6 months was 0.85, equivalent to the AUC of 0.83 observed with the GCS (65). The FOUR scale allows the explicit testing of eye movements or blinking that facilitates the detection of locked-in state or the transition from VS to MCS. However, the usefulness of a scale that excludes verbal assessment could be debated especially in the TBI population, the majority of whom have moderate or mild injury in which a critical distinguishing feature is verbal performance. Furthermore, respiratory patterns

FOUR Scale	GCS
Eye opening	**Eye opening**
4 = eyelids open or opened, tracking, or blinking to command	4 = eyes open spontaneously
3 = eyelids open but not tracking	3 = eye opening to verbal command
2 = eyelids closed but open to loud voice	2 = eye opening to pain
1 = eyelids closed but open to pain	1 = no eye opening
0 = eyelids remain closed with pain	
Motor response	**Motor response**
4 = thumbs-up, fist, or peace sign	6 = obeys commands
3 = localizing to pain	5 = localizing pain
2 = flexion response to pain	4 = withdrawal from pain
1 = extension response to pain	3 = flexion response to pain
0 = no response to pain or generalized myoclonus status	2 = extension response to pain
	1 = no motor response
Brainstem reflexes	**Verbal response**
4 = pupil and corneal reflexes present	5 = oriented
3 = one pupil wide and fixed	4 = confused
2 = pupil or corneal reflexes absent	3 = inappropriate words
1 = pupil and corneal reflexes absent	2 = incomprehensible sounds
0 = absent pupil, corneal, and cough reflex	1 = no verbal response
Respiration	
4 = not intubated, regular breathing pattern	
3 = not intubated, Cheyne-Stokes breathing pattern	
2 = not intubated, irregular breathing	
1 = breathes above ventilator rate	
0 = breathes at ventilator rate or apnea	

Figure 2. Comparison of the Full Outline of UnResponsiveness (FOUR) scale with the Glasgow Coma Scale (GCS). Adapted from Wijdicks et al (64).

can be difficult to interpret in patients undergoing mechanical ventilation. These characteristics suggest that the clinical utility of the FOUR scale may be more relevant in the postacute phase of SBI.

Neuroimaging

Several features readily identified on cranial CT scan have major prognostic significance. These include shift of midline structures, encroachment of the basal cisterns, cerebral infarction, subarachnoid hemorrhage, intraventricular hemorrhage, diffuse injury, and extra-axial hematomas (66–69). Widespread availability and speed of image processing have established CT as a cornerstone in the evaluation and outcome prediction of patients with TBI. However, CT lacks the resolution to correctly identify or characterize smaller white matter lesions as they might occur in the setting of diffuse axonal injury (70).

The significance of brain MRI as a prognostic tool in the acute setting of TBI is being actively investigated (71). MRI sequences such as diffusion weighted imaging and susceptibility weighted imaging are potentially more sensitive to diffuse axonal injury and have been shown to increase the accuracy of outcome prediction (72–74). Recent work indicates that diffusion tensor imaging (DTI) is highly sensitive to traumatic white matter damage (75) and is predictive of long-term functional outcome (76, 77). In a prospective evaluation of 105 patients who were comatose 1–3 weeks after TBI, a prognostic score that integrated DTI measurements of white matter tracts with the IMPACT score was able to classify 1-year functional outcomes with greater accuracy than the IMPACT score alone (78). Using early proton magnetic resonance spectroscopy, it is possible to identify axonal loss (reduced N-acetyl aspartate-to-creatine ratio) and increased myelin turnover (increased choline-to-creatine ratio) in the tissue that appears normal using conventional morphological MRI sequences (79), changes that have been linked to worse long-term outcome (76, 79, 80).

Brain Physiology and Metabolism

Sustained elevations of intracranial pressure (ICP) to greater than 20 mm Hg or decreases in cerebral perfusion pressure (CPP) to less than 50–60 mm Hg have been linked with cerebral infarction, herniation, and death following TBI (69, 81). Studies indicate that changes in ICP cannot be predicted in a reliable or timely manner with clinical assessment or imaging (82–85); however, the efficacy of ICP-guided management has been challenged (86–88). Brain tissue monitoring indicates that even when ICP and CPP are within normal limits, significant reductions in brain tissue oxygen pressure ($Pbto_2$) may occur, and brain tissue hypoxia has been associated with worse outcome (89, 90). Consistent with these observations, studies suggest beneficial effects of clinical algorithms that target normalization of $Pbto_2$ levels (91–93). Similarly, the use of cerebral microdialysis probes demonstrates neurometabolites in the brain interstitium whose concentrations have been associated with outcome following neurologic trauma (94, 95). In the largest of these studies, a cohort of 223 patients with severe TBI, low brain extracellular glucose and elevated lactate to pyruvate (L/P) were independently predictive of mortality at 6 months (96). Microdialytic assessment may identify irreversible neuronal loss, as indicated in a study that found an association between elevations in L/P in the acute setting and subsequent volume loss in the frontal lobes (97). Preliminary microdialysis studies in patients with severe TBI suggest that brain extracellular concentrations of amyloid fragments, tau protein, and neurofilament heavy chain protein may also have prognostic significance (98–100).

Electrophysiology

The use of continuous electroencephalography (cEEG) suggests that seizure activity and status epilepticus, often clinically

undetected, occur in a significant number of patients with severe TBI, and such perturbations have been linked to outcome (101, 102). In a study of 94 patients with moderate to severe TBI who underwent cEEG monitoring, seizures occurred in 21, and mortality was 100% in patients with status epilepticus (103). Seizures following TBI are associated with increased cerebral metabolic rate, cerebral blood flow and volume, and increasing ICP in susceptible patients (104). It has been suggested that seizures cause injury, compounding trauma-induced damage: hippocampal atrophy was more pronounced in TBI patients with seizures than in those without seizures, and atrophy was most apparent on the hippocampus ipsilateral to the seizure focus (105). Additional research is needed to determine if early and intensive suppression of seizure activity or periodic discharges may improve outcome after TBI; current guidelines recommend 7 days of seizure prophylaxis following moderate to severe TBI (106).

The value of somatosensory evoked potentials (SSEPs) in predicting outcome of severe TBI was evaluated in a meta-analysis of 44 studies published from 1976 to 2000 (107). The bilateral absence of cortical signals on SSEP had a positive predictive value of 98.7% in predicting adverse outcome 2 months to 3 years after head injury; however, the accuracy of prediction is significantly lower when patients have focal lesions, subdural fluid collections, and recent decompressive surgery (107). In a more recent report, bilaterally absent cortical SSEP responses assessed on the third day after severe TBI were correlated with functional outcomes at 1 year; furthermore, SSEP helped predict performance on tests of information-processing speed, working memory, and attention 1 year after injury (108).

Serum Biomarkers

Serum levels of S100 beta protein and neuron-specific enolase (NSE), markers of glial and neuronal damage, respectively, have been extensively studied in patients with TBI. In some studies, these markers correlated with findings on neuroimaging but were not independently predictive of specific outcomes (109–111). Other investigations have indicated that S100 beta and NSE have value not only in determining the severity of TBI but also in classifying their outcomes (112–119). Glial fibrillary acidic protein (GFAP) is specific to glial cells in the central nervous system, and increased levels are detectable in the serum of patients with acquired brain injury. Studies suggest that serum GFAP levels correlate with clinical and neuroradiologic injury severity and are significantly higher in patients who die or have poor functional outcome (116, 119–121). The predictive value of other serum biomarkers, in particular tau protein, is still under investigation (122, 123).

Systemic Biochemical Variables

Several studies have investigated associations of routinely measured laboratory parameters and outcome in patients with TBI. Among them, coagulation disturbances, low platelet counts, as well as anemia, hypoalbuminemia, elevated serum creatinine, and high serum glucose concentrations have been associated with adverse outcomes in both univariate and multivariate models (63, 124–129). Given the adverse association of high glucose concentrations with outcome, recent randomized trials have evaluated intensive insulin therapy to maintain normoglycemia in TBI patients; however, a distinct outcome benefit was not demonstrated (130–132). Other studies using cerebral microdialysis have found that intensive insulin therapy may result in unfavorable trends in brain extracellular glucose and L/P ratios (133–135). In a randomized crossover trial of intensive (80–110 mg/dL) vs. less intensive (120–150 mg/dL) glycemic control in 13 patients with severe TBI, critical reductions in brain interstitial glucose and elevations of L/P ratio were more frequent in patients allocated to intensive glycemic control and were associated with increased [18F]-deoxy-D-glucose uptake on PET (136). Given data linking poor glycemic control and adverse head injury outcome (63, 129), additional studies are needed to evaluate whether increased brain glucose delivery via carefully titrated moderate hyperglycemia represents a viable strategy in severe TBI.

Therapeutic Intervention

Evidence suggests that prognosis of TBI may be favorably influenced by rigorous supportive management and enhancements in the process of care. Aggressive measures to normalize oxygenation, volume status, and blood pressure in the early stages of injury have been linked to improved outcome (137–139), as those measures are used in high-volume trauma centers and protocol-driven medical management (140, 141). However, studies favoring these interventions are associative in nature, and direct evidence of their causal effect on the biology and natural history of TBI is lacking.

Although preclinical data on therapeutic hypothermia as a neuroprotectant have been encouraging, a beneficial effect on post-TBI neurological and functional outcomes has not been confirmed in human randomized trials (142, 143). Hypothermia may have greater value in the management of intracranial hypertension. In a systematic review of hypothermia trials in TBI, four of five studies targeting ICP elevation reported a decrease in mortality or in the percentage of patients having a poor recovery, whereas none of the three studies in which hypothermia was assessed as a neuroprotectant showed any benefit (144).

PROGNOSIS AFTER CA

In contrast to the IMPACT and CRASH models for TBI, predictive scoring systems have not been validated in patients with hypoxic-ischemic encephalopathy following CA. Prognosis is preponderantly based on associations derived from physical examination, electrophysiological tests, neuroimaging, and biomarkers. In a statement published in 2006, the American Academy of Neurology expert panel generated recommendations regarding outcome prediction in comatose survivors of CA (145). Based on a review of the literature, the panel concluded that unfavorable outcome can be predicted 72 hours post-CA on the basis of absent pupillary or corneal responses,

TABLE 3. Predictive Value of Clinical Examination in Hypoxic-Ischemic Brain Injury

Reference/ Country	Study Design	Patients or Studies	Time of Examination	Assessment	Definition of Poor Outcome	Prediction of Poor Outcome
Pupillary or corneal reactivity						
Zandbergen et al (199)/The Netherlands	Systematic review	33 studies	In the first 3 d after CPR	Absence of pupillary reactivity	Death or vegetative state	False-positive rate 9%
Booth et al (200)/ Canada	Systematic review	11 studies	In the first 24 hr after CPR	Absence of pupillary reactivity	CPC 3–5	Likelihood ratio 10.2; 95% CI 1.8–48.6
Zandbergen et al (173)/The Netherlands	Prospective study	407 patients from 32 ICUs	In 12, 24, and 72 hr after CPR	Absence of pupillary or corneal reactivity	Death or vegetative state at 1 mo	False-positive rate 4% at 12 hr, 2% at 24 hr, 0% at 72 hr
Wijdicks et al (145)/United States	Systematic review	12 studies	In the first 3 d after CPR	Absence of pupillary reactivity	Death or coma after 1 mo or death, coma, or severe disability requiring nursing care after 6 mo	False-positive rate 0%
Al Thenayan et al (201)/ Canada	Retrospective study	37 patients	At day 3 after CPR and hypothermia	Absence of pupillary or corneal reactivity	No recovery of awareness during hospital stay	False-positive rate 0%
Rossetti et al (202)/ Switzerland	Prospective study	111 patients	In the first 3 d after CPR and hypothermia	Absence of brainstem reflexes	Death during hospital stay	False-positive rate 4%
Fugate et al (187)/United States	Prospective study	103 patients	At day 3 after CPR and hypothermia	Absence of pupillary or corneal reactivity	Death during hospital stay	False-positive rate 0%
Bouwes et al (189)/The Netherlands	Prospective multicenter study (ten centers)	196 patients with pupillary tests; 130 with corneal tests	In the first 3 d after CPR	Absence of pupillary or corneal reactivity	GOS 1–3 at 6 mo	False-positive rate 1% for pupils; 4% for cornea
Rossetti et al (190)/ Switzerland	Prospective study	61 patients	After CPR and hypothermia	Absence of brainstem reflexes	CPC 3–5 at 3 mo	False-positive rate 11%
Motor responses						
Zandbergen et al (199)/ Netherlands	Systematic review	33 studies	In the first 3 d after CPR	Absence of motor responses	Death or vegetative state	False-positive rate 7%
Booth et al (200)/ Canada	Systematic review	1,914 patients from 11 studies	In the first 3 d after CPR	Absence of motor responses	CPC 3–5	Likelihood ratio 9.2; 95% CI 2.1–49.4
Zandbergen et al (173)/The Netherlands	Prospective study	407 patients from 32 ICUs	At 12, 48, and 72 hr after CPR	Absence of motor responses	Death or vegetative state at 1 mo	False-positive rate 9% at 12 hr, 6% at 24 hr, 5% at 72 hr

(*Continued*)

TABLE 3. (*Continued*). Predictive Value of Clinical Examination in Hypoxic-Ischemic Brain Injury

Reference/ Country	Study Design	Patients or Studies	Time of Examination	Assessment	Definition of Poor Outcome	Prediction of Poor Outcome
Wijdicks et al (145)/United States	Systematic review	12 studies	In the first 3 d after CPR	GCS motor score 1–2	Death or coma after 1 mo or death, coma, or severe disability requiring nursing care after 6 mo	False-positive rate 0%
Al Thenayan et al (201)/ Canada	Retrospective study	37 patients	At day 3 after CPR and hypothermia	Motor response no better than extension	No recovery of awareness during hospital stay	False-positive rate 14%
Rossetti et al (202)/ Switzerland	Prospective study	111 patients	In the first 3 d after CPR and hypothermia	Absence of motor responses	Death during hospital stay	24% with false-positive mortality predictions during hypothermia
Fugate et al (187)/United Stated	Prospective study	70 patients (of 103)	At day 3 after CPR and hypothermia	Motor response no better than extension	Death during hospital stay	False-positive rate 3%
Bouwes et al (189)/The Netherlands	Prospective multicenter study (ten centers)	284 patients (of 391)	At day 3 after CPR and hypothermia	Motor response no better than extension	GOS 1–3 at 6 mo	False-positive rate 10%
Rossetti et al (190)/ Switzerland	Prospective study	61 patients	After CPR and hypothermia	Extension or no motor response	CPC 3–5 at 3 mo	False-positive rate 7%
Myoclonus						
Wijdicks et al (203)/United States	Prospective study	107 patients	After CPR	Presence of myoclonus	Death during hospital stay	False-positive rate 0%
Zandbergen et al (173)/The Netherlands	Prospective study	407 patients from 32 ICUs	In first 3 d after CPR	Presence of myoclonus	Death or vegetative state at 1 mo	False-positive rate 0%
Wijdicks et al (145)/United States	Systematic review	12 studies	In the first 3 d after CPR and hypothermia	Presence of myoclonus	Death or coma after 1 mo or death, coma, or severe disability requiring nursing care after 6 mo	False-positive rate 0%
Al Thenayan et al (201)/ Canada	Retrospective study	37 patients	At day 3 after CPR and hypothermia	Presence of myoclonus	No recovery of awareness during hospital stay	False-positive rate 0%
Rossetti et al (202)/ Switzerland	Prospective study	111 patients	In the first 3 d after CPR and hypothermia	Presence of myoclonus	Death during hospital stay	7% with false-positive mortality predictions during hypothermia
Fugate et al (187)/United States	Prospective study	103 patients	At day 3 after CPR and hypothermia	Presence of myoclonus	Death during hospital stay	False-positive rate 0%
Rossetti et al (190)/ Switzerland	Prospective study	61 patients	After CPR and hypothermia	Presence of myoclonus	CPC 3–5 at 3 mo	False-positive rate 7%

CPR = cardiopulmonary resuscitation; CPC = Cerebral Performance Categories Scale; GOS = Glasgow Outcome Scale; CI = confidence interval; GCS = Glasgow Coma Scale.

TABLE 4. Predictive Value of Neuron-Specific Enolase for Poor Outcome in Hypoxic-Ischemic Brain Injury

Reference/ Country	Study Design	Patients or Studies	Time of Examination	Assessment	Definition of Poor Outcome	Prediction of Poor Outcome
NSE						
Zandbergen et al (204)/The Netherlands	Systematic review	802 patients from 28 studies	After CPR	NSE in cerebrospinal fluid > 33 ng/mL	Death or persistent vegetative state	False-positive rate 0%
Meynaar et al (185)/ Netherlands	Prospective study	110 patients	At 6 hr after CPR	Serum NSE > 25 ng/mL	Death or no recovery from coma until discharge	False-positive rate 0%
Zingler et al (205)/ Germany	Prospective study	27 patients	At days 1, 2, 3, and 7 after CPR	Serum NSE at different cutoffs	CPC 3–5 at 3 mo	False-positive rate 0% at different cutoffs on all days
Tiainen et al (186)/ Finland	Prospective study	70 patients	At 24 and 36 hr after CPR with or without hypothermia	Serum NSE at different cutoffs	CPC 3–5 at 6 mo	At all time points and all cutoffs false-positive rate 0% in patients without, 4% in patients with hypothermia. Lower levels with hypothermia
Zandbergen et al (173)/The Netherlands	Prospective study	407 patients from 32 ICUs	At 24, 48, and 72 hr after CPR	Serum NSE > 33 ng/mL	Death or vegetative state at 1 mo	False-positive rate 0% at all time points
Wijdicks et al (145)/ United States	Systematic review	12 studies	At day 3 after CPR	Serum NSE at different cutoffs	Death or coma after 1 mo or death, coma, or severe disability requiring nursing care after 6 mo	False-positive rate 0% at different cutoffs
Fugate et al (187)/ United States	Prospective study	74 patients (of 103)	At day 3 after CPR and hypothermia	Serum NSE > 33 ng/mL	Death during hospital stay	False-positive rate 29%
Steffen et al (188)/ Germany	Prospective study	230 patients	At 72 h after CPR with and without hypothermia	Serum NSE at different cutoffs	CPC 3–5 at discharge	ROC analysis: higher cutoff with a false-positive rate 0% in hypothermia (78.9 ng/mL) compared to no hypothermia (26.9 ng/mL)
Cronberg et al (206)/ Sweden	Prospective study	34 patients (of 111)	At 48 hr after CPR and hypothermia	Serum NSE > 33 ng/mL	CPC 3–5 at 6 mo	False-positive rate 0%
Bouwes et al (189)/The Netherlands	Prospective multicenter study (ten centers)	391 patients	At 12, 36, and 48 hr after CPR and hypothermia	Serum NSE > 33 ng/mL	GOS 1–3 at 6 mo	False-positive rate 10% at 12 hr, 9% at 36 hr, and 7% at 48 hr
Rossetti et al (190)/ Switzerland	Prospective study	61 patients	At 24 and 48 hr after CPR and hypothermia	Serum NSE > 33 ng/mL	CPC 3–5 at 3 mo	False-positive rate 4%

CPR = cardiopulmonary resuscitation; NSE = neuron-specific enolase; ROC = receiver operating characteristic; CPC = Cerebral Performance Categories Scale; GOS = Glasgow Outcome Scale.

TABLE 5. Predictive Value of Electrophysiological Assessment in Hypoxic-Ischemic Brain Injury

Reference/ Country	Study Design	Patients or Studies	Time of Examination	Assessment	Definition of Poor Outcome	Prediction of Poor Outcome
Somatosensory evoked potentials						
Chen et al (167)/ Canada	Prospective case series	34 patients	In the first 3 d after CPR	Bilateral absence of N20	No recovery, coma until death or persistent vegetative state	False-positive rate 0%
Pohlmann-Eden et al (207)/ Germany	Prospective study	42 patients	After 36 hr after CPR	Bilateral absence of N20	GOS 3–5 at 3 mo	False-positive rate 3%
Zandbergen et al (199)/The Netherlands	Systematic review	33 studies	In the first week after CPR	Bilateral absence of N20	Death or vegetative state	False-positive rate 0%
Meynaar et al (185)/The Netherlands	Prospective study	59 patients (of 110)	At ≥ 48 hr after CPR	Bilateral absence of N20	Death or no recovery from coma until discharge	False-positive rate 0%
Zandbergen et al (173)/The Netherlands	Prospective study	407 patients from 32 ICUs	At 24, 48, and 72 hr after CPR	Bilateral absence of N20	Death or vegetative state at 1 mo	False-positive rate 0% for all time points
Wijdicks et al (145)/United States	Systematic review	12 studies	At day 3 after CPR	Bilateral absence of N20	Death or coma after 1 mo or death, coma, or severe disability requiring nursing care after 6 mo	False-positive rate 0%
Bouwes et al (208)/The Netherlands	Prospective multicenter study (two centers)	77 patients	After CPR and during hypothermia	Bilateral absence of N20	GOS 1–2 at 1 mo	False-positive rate 0% during hypothermia
Rossetti et al (202)/ Switzerland	Prospective study	111 patients	In the first 3 d after CPR and hypothermia	Bilateral absence of N20	Death during hospital stay	False-positive rate 0%
Fugate et al (187)/United States	Prospective study	14 patients (of 103)	After CPR and during hypothermia	Bilateral absence of N20	Death during hospital stay	False-positive rate 0% during hypothermia
Leithner et al (209)/ Germany	Retrospective study	112 patients (of 185)	After CPR and during hypothermia	Bilateral absence of N20	CPC 3–5 at discharge	1/36 patients with absent early N20 had good outcome during hypothermia
Bouwes et al (189)/The Netherlands	Prospective multicenter study (ten centers)	391 patients	After CPR and during and after hypothermia	Bilateral absence of N20	GOS 1–3 at 6 mo	False-positive rate 3% during hypothermia; 0% after hypothermia
Rossetti et al (190)/ Switzerland	Prospective study	61 patients	After CPR and hypothermia	Bilateral absence of N20	CPC 3–5 at 3 mo	False-positive rate 0%

(*Continued*)

TABLE 5. (*Continued*). Predictive Value of Electrophysiological Assessment in Hypoxic-Ischemic Brain Injury

Reference/ Country	Study Design	Patients or Studies	Time of Examination	Assessment	Definition of Poor Outcome	Prediction of Poor Outcome
EEG patterns						
Chen et al (167)/ Canada	Prospective case series	34 patients	In the first 3 d after CPR	Suppression, unreactive alpha/theta, epileptiform discharges, burst-suppression.	No recovery, coma until death or persistent vegetative state	Two patients had good outcome
Zandbergen et al (199)/The Netherlands	Systematic review	33 studies	After CPR	EEG burst-suppression or isoelectric trace	Death or vegetative state	False-positive rate 9%
Zandbergen et al (173)/The Netherlands	Prospective study	407 patients from 32 ICUs	After CPR	EEG burst-suppression or isoelectric curve; postanoxic status epilepticus	Death or vegetative state at 1 mo	False-positive rate 0% for EEG burst-suppression or isoelectric curve; false-positive rate for 7% postanoxic status epilepticus
Wijdicks et al (145)/United States	Systematic review	12 studies	After CPR	EEG burst-suppression or generalized epileptiform discharges	Death or coma after 1 mo or death, coma, or severe disability requiring nursing care after 6 mo	False-positive rate 3%
Rossetti et al (210)/ Switzerland	Retrospective study	107 patients (of 166)	After CPR with and without hypothermia	Postanoxic status epilepticus	Death during hospital stay	False-positive rate 8%
Rossetti et al (171)/ Switzerland	Prospective study	34 patients	After CPR and during hypothermia	cEEG burst-suppression, seizures or epileptiform discharges	Death during hospital stay	False-positive rate 0% during hypothermia
Rossetti et al (202)/ Switzerland	Prospective study	111 patients	In the first 3 d after CPR and hypothermia	EEG epileptiform activity	Death during hospital stay	False-positive rate 9%
Fugate et al (187)/United States	Prospective study	21 patients (of 103)	At day 3 after CPR and hypothermia	EEG burst-suppression or isoelectric curve. Status epilepticus or no background reactivity	Death during hospital stay	False-positive rate 0%
Thenayan et al (211)/Saudi Arabia	Retrospective study	29 patients	After CPR with and without hypothermia	EEG with generalized suppression or burst-suppression	No recovery of awareness during hospital stay	False-positive rate 0%
Rossetti et al (190)/ Switzerland	Prospective study	61 patients	After CPR and during hypothermia	Epileptiform transients	CPC 3–5 at 3 mo	False-positive rate 0% during hypothermia

(*Continued*)

TABLE 5. (*Continued*). Predictive Value of Electrophysiological Assessment in Hypoxic-Ischemic Brain Injury

Reference/ Country	Study Design	Patients or Studies	Time of Examination	Assessment	Definition of Poor Outcome	Prediction of Poor Outcome
EEG background reactivity						
Rossetti et al (171)/ Switzerland	Prospective study	34 patients	After CPR and during hypothermia	Absence of cEEG background reactivity	Death during hospital stay	False-positive rate 0% during hypothermia
Rossetti et al (202)/ Switzerland	Prospective study	111 patients	In the first 3 d after CPR and hypothermia	Absence of EEG background reactivity	Death during hospital stay	False-positive rate 7%
Thenayan et al (211)/ Saudi Arabia	Retrospective study	29 patients	After CPR and with or without hypothermia	Preserved EEG background reactivity	No recovery of awareness during hospital stay	10/11 patients with reactivity regained awareness
Rossetti et al (190)/ Switzerland	Prospective study	61 patients	After CPR and during hypothermia	Absence of EEG background reactivity	CPC 3–5 at 3 mo	False-positive rate 0% during and after hypothermia
Howard et al (212)/United Kingdom	Retrospective study	39 patients	At a mean of 5 d after CPR	Absence of EEG background reactivity or periodic generalized phenomenon	Death, profound cognitive impairment, including persistent vegetative state, minimally area states, or severe physical impairment at discharge	Significant association with poor outcome (false-positive rate not provided)

CPR = cardiopulmonary resuscitation; EEG = electroencephalography; cEEG = continuous electroencephalography; GOS = Glasgow Outcome Scale; CPC = Cerebral Performance Categories Scale.

or absent or extensor motor response (**Table 3**). The panel also pointed to myoclonus status epilepticus, elevated serum NSE (**Table 4**), and absent cortical response of SSEPs (**Table 5**) as additional predictive elements. These recommendations were exclusively based on studies of patients who were not treated with therapeutic hypothermia.

Prognostication following CA has been considered in terms of prearrest factors, intra-arrest factors, and postresuscitation factors (6, 146). Prearrest factors include age, race, Acute Physiology and Chronic Health Evaluation II and III scores, diabetes mellitus, sepsis, metastatic cancer, renal failure, homebound lifestyle, and stroke; these factors have been linked with outcome but are not reliable prognostic variables (6). Intra-arrest factors include the duration of time between circulatory collapse and the start of cardiopulmonary resuscitation (CPR), duration of CPR to return of spontaneous circulation, asystole, noncardiac causes of arrest, nonadherence to established CPR guidelines, and maximum end-tidal carbon dioxide (ET_{CO_2}) of less than 10 mm Hg—all linked to unfavorable outcome. Postresuscitation factors are discussed below.

There is a need for large-scale prospective studies designed to validate the individual and integrated significance of clinical, biochemical, electrophysiological, and imaging variables in predicting CA outcome. Meanwhile, existing recommendations regarding prognostication should be applied with caution in CA patients treated with hypothermia, as the accuracy of tests during and after hypothermia has been seriously challenged. An approach for prognostication in CA patients treated with hypothermia is shown in **Figure 3**.

Clinical Assessment

As in patients with TBI, outcome prediction in hypoxic-ischemic encephalopathy is heavily reliant on clinical assessment. In a landmark early study conducted in patients with coma from a range of nontraumatic etiologies, unfavorable 1-year outcome could be predicted on the basis of a limited number of clinical signs, including the inability to follow commands, the lack of visual fixation or pursuit,

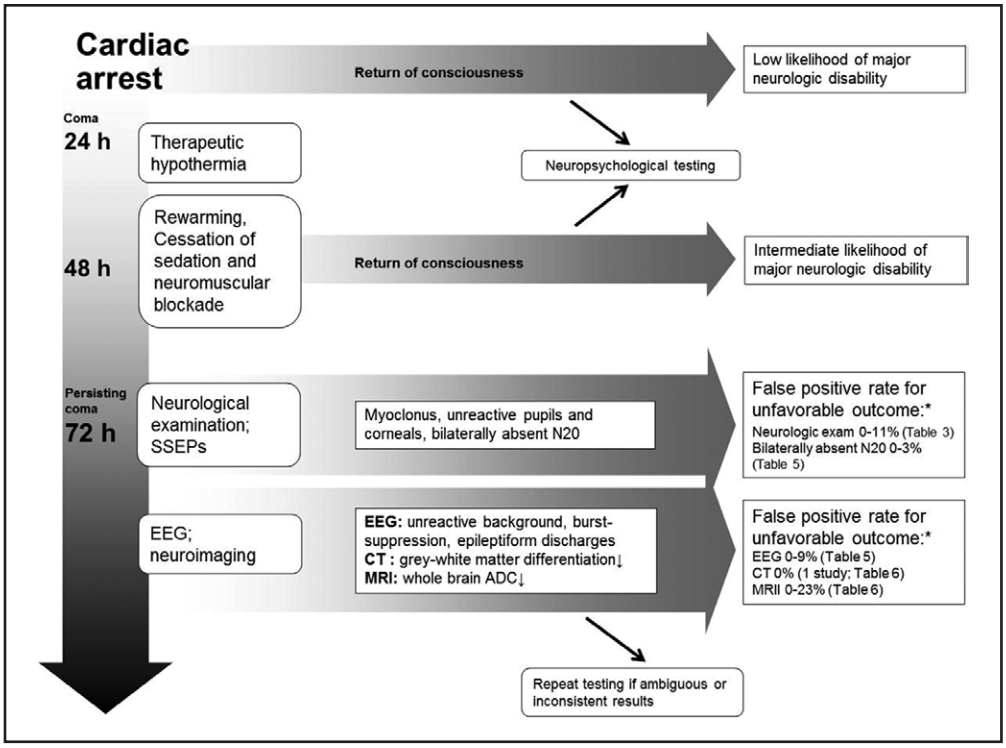

Figure 3. Proposed algorithm for prognostication in hypoxic-ischemic brain injury. SSEPs = somatosensory evoked potentials; FPR = false-positive rate; EEG = electroencephalography; ADC = apparent diffusion coefficient; cEEG = continuous electroencephalography; NSE = neuron-specific enolase; ROSC = return of spontaneous circulation. *Definitions of unfavorable outcome are presented in Tables 3–6.

and the lack of oculocephalic or oculovestibular responses (147). These results and additional analysis in a subset of patients with hypoxic-ischemic encephalopathy (148) are the evidentiary basis for a widely cited practice guideline from the American Academy of Neurology (145). In a more recent cohort of 500 patients, the pupillary and, to a lesser degree, oculocephalic responses were the clinical findings most predictive of 6-month functional outcome (149). Current prospective evaluations in CA patients who have been treated with hypothermia seriously challenge the prognostic accuracy of selected clinical findings, in particular the association between absent or abnormal motor responses and poor outcome, with false-positive rates of 10% and 24% in two recent reports (150, 151).

Neuroimaging

Neuropathological studies of patients who died following CA indicate neuronal death that is prominent in occipital, frontal, and parietal cortex; the hippocampus; the basal ganglia; the thalamic reticular nucleus; Purkinje cells of the cerebellum; and the spinal cord (152). When evaluated with cranial CT, early hypoxic-ischemic damage may be suggested by a loss of differentiation between gray and white matter (153, 154); however, in many cases, CT is unrevealing. With brain MRI, early reports demonstrated multifocal cortical (155) or white matter changes (156) that were associated with poor outcome following CA (155–157). More recently, the prognostic value of quantitative diffusion-weighted MRI has been studied in CA survivors (158–160). In a prospective evaluation of 51 patients, one group found that whole-brain apparent diffusion coefficients (ADCs) derived from MRI 49 to 108 hours after CA accurately classified 6-month functional outcome, surpassing the sensitivity of clinical neurological assessment (159). Related studies indicate that unfavorable outcome might be predicted by reduced regional ADC values in the putamen and in occipital, parietal, and temporal cortices (158, 161) (**Table 6**). In a recent prospective evaluation of 57 CA patients, it was found that a prognostic model based on a quantitative DTI assessment of white matter tracts predicted the 1-year functional outcome with a high degree of accuracy (162). Anecdotal reports in patients with CA indicate that brain proton magnetic resonance spectroscopy identifies metabolic abnormalities associated with neuronal and glial cell damage; however, the prognostic significance of these findings requires further study (163, 164).

Electrophysiologic Tests

Seizures are detected in up to 40% of comatose survivors of CA and have been linked to adverse outcome (146, 148, 165, 166). Malignant EEG patterns, such as burst-suppression, nonreactive, or flat-line EEG, are powerful indicators of unfavorable prognosis (167–169); however, these findings have reduced specificity in patients treated with hypothermia (150, 151), a limitation that may be overcome with the help of quantitative EEG methods (170). Recently, the presence of background EEG reactivity in response to a noxious stimulus was identified as an important new predictor of favorable outcome (151, 171) (Table 5).

Available studies indicate that short-latency SSEPs have robust prognostic value in patients after CA; the bilateral absence of the cortical N20 potential has a specificity of close to 100% for the prediction of poor outcome (145, 146, 167, 172–174) (Table 5). While absent or abnormal N20 signals are validated predictors of poor outcome, it has been hypothesized that long-latency potentials (e.g., P300 and mismatch negativity [MMN]), which evaluate the functional integrity of corticocortical and thalamocortical circuits, might be best suited to predict coma emergence and higher order cognitive function

TABLE 6. Predictive Values of Neuroimaging for Poor Outcome in Hypoxic-Ischemic Brain Injury

Reference/ Country	Study Design	Patients or Studies	Time of Examination	Assessment	Definition of Poor Outcome	Prediction of Poor Outcome
Wijdicks et al (155)/ United States	Prospective study	27 patients	In the first 15 d after CPR	Brain MRI with diffuse signal abnormalities in the cortex and subcortical areas or effacement of the sulci	Death during hospital stay	All eight patients with these MRI findings died; one of two patients who survived had subcortical signs of ischemia
Wu et al (158)/ United States	Retrospective study	80 patients	In first 7 d after CPR and hypothermia	Brain MRI with lower whole brain and regional median ADC	mRS 3–6 at 6 mo	Patients with mRS >3 had significant lower median whole brain and regional ADC
Topcuoglu et al (213)/ Turkey	Prospective study	22 patients	At a median 4.1d (good outcome) and 9.8 d (poor outcome) after CPR	Brain MRI with DWI and FLAIR with lesion pattern of multilobar, or diffuse, cortical involvement	CPC 4–5 at discharge	False-positive rate 0%
Wijman et al (159)/ United States	Prospective study	40 patients (of 83)	In the first 7 d after CPR and hypothermia	Brain MRI with ADC $< 650 \times 10^6$ mm^2/s	Death during hospital stay	False-positive rate 0%
Fugate et al (187)/ United States	Prospective study	53 patients (of 103)	At a median 1 d after CPR and hypothermia	Brain CT with global edema	Death during hospital stay	False-positive rate 0%
Choi et al (160)/ Korea	Prospective study	22 patients (of 111)	At 48 hr after CPR and hypothermia	Brain MRI with global ischemia or focal ischemia with total lesion volume >20 mL	CPC 3–5 at 6 mo	False-positive rate 0%
Cronberg et al (206)/ Sweden	Prospective study	39 patients	In the first 5 d after CPR and hypothermia	Brain MRI with cortical and/or deep gray nuclei lesions	GOS 1–3 at 3 mo	False-positive rate 23%
Howard et al (212)/ United Kingdom	Retrospective study	39 patients	Between 1 and 150 d after CPR	Brain MRI with extensive changes in cortex and the deep gray matter on DWI and T2-weighted imaging	Death, profound cognitive impairment including persistent vegetative state, minimally area states or severe physical impairment at discharge	False-positive rate 0%

CPR = cardiopulmonary resuscitation; DWI = diffusion weighted imaging; ADC = apparent diffusion coefficient; FLAIR = fluid-attenuated inversion recovery; mRS = modified Ranking Scale; CPC = Cerebral Performance Categories Scale; GOS = Glasgow Outcome Scale.

(175, 176). The MMN reflects cortical discrimination of an "oddball" stimulus within a series of identical sounds (177). In a seminal report on 62 comatose CA survivors, all patients in whom MMN was present recovered consciousness (178). In a prospective nonrandomized comparison, the amplitude of the P300 response was significantly higher in CA patients who received therapeutic hypothermia than in those who were normothermic (179).

Serum Biomarkers

Serum and cerebrospinal fluid markers, NSE and S100 beta in particular, have been evaluated in patients with hypoxic-ischemic encephalopathy (180–184). Older studies indicated that elevations in serum NSE were robustly associated with poor outcome (146, 185, 186). More recent work indicates that the accuracy of serum NSE elevation in patients who received therapeutic hypothermia is significantly reduced, with false-positive rates of 4% to 29% (Table 4) (187–190). The prognostic significance of other serum biomarkers is less well studied. Preliminary data suggest that serum GFAP accurately discriminates prognostic categories following CA (191) and that serum procalcitonin may classify outcome with greater accuracy than GFAP (192). In a very recent study, serum levels of tau protein were highly predictive of 6-month post-CA functional outcome (193).

Therapeutic Interventions

Lowering of body temperature to 32°–34°C during the first hours after CA reduces neurologic injury by concurrently disrupting a range of pathological cellular events (194, 195). Two randomized trials published in 2002 demonstrated that therapeutic hypothermia implemented early after CA reduces mortality and significantly improves functional outcome (4, 5). In the Hypothermia After Cardiac Arrest Study, 55% of the cooled patients had favorable functional outcomes at 6 months compared with 39% of normothermic control patients (5); these results were confirmed in a contemporary study from Australia (4). Based on preliminary findings, it was postulated that a shorter delay to reach target temperature would lead to improved functional outcome; however, this was not verified in two recent randomized trials (196, 197).

Therapeutic hypothermia, possibly the first targeted intervention in SBI with an unequivocal outcome-modifying effect, has not surprisingly challenged older principles of CA prognostication. Prior to the era of hypothermia, selected variables were recognized as accurate predictors of poor outcome when observed or measured 72 hours after CA, particularly the absence of brainstem reflexes, the presence of extensor motor responses, and a serum NSE level greater than 33 ng/mL (145). Recent studies in patients treated with hypothermia indicate that these same variables fail to accurately discriminate outcome categories, with unacceptably high false-positive rates for the prediction of poor outcome when used in the same time frame as the older studies (Tables 3–6). Emerging evidence suggests that hypothermia modifies the time course of post-CA neurologic injury and recovery. It follows that the determination of a CA prognosis, traditionally ascertained at 72 hours, in all likelihood, must be deferred to a later time point. However, there are insufficient data to recommend specifically when prognostic assessment should be made (198). Large prospective studies are needed to build prediction models integrating the neurologic examination and electrophysiological and neuroimaging assessments for outcome after CA.

CONCLUSIONS

In patients with SBI, the goal of accurate and reliable prognosis is to guide treatment strategies, so that they are proportionate with outcome. Models for outcome prediction include data from clinical assessment; physiological status; and laboratory, neuroimaging, and electrophysiological examinations. Existing prognostic systems need to be revised, as treatment strategies, such as therapeutic hypothermia, reduce their predictive value. In addition, determinants of outcome, such as genetic susceptibility and biological heterogeneity, need to be rigorously evaluated. Integration of these factors is likely to increase the accuracy of prognostic models in patients suffering from SBI.

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