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REVIEW ARTICLE

Cardiology

Neurologic prognostication after resuscitation from cardiac arrest

Joshua R. Lupton MD, MPH[1] | **Michael C. Kurz MD**[2] | **Mohamud R. Daya MD**[1]

[1] Oregon Health and Science University, Portland, Oregon, USA

[2] University of Alabama-Birmingham, Birmingham, Alabama, USA

Correspondence
Joshua Lupton, MD, MPH, MPhil, Department of Emergency Medicine, Center for Policy and Research in Emergency Medicine, Oregon Health & Science University, 3181 SW Sam Jackson Park Road, Portland, OR 97239-3098, USA.
Email: lupton@ohsu.edu

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Abstract

Out-of-hospital cardiac arrest remains a leading cause of mortality in the United States, and the majority of patients who die after achieving return of spontaneous circulation die from withdrawal of care due to a perceived poor neurologic prognosis. Unfortunately, withdrawal of care often occurs during the first day of admission and research suggests this early withdrawal of care may be premature and result in unnecessary deaths for patients who would have made a full neurologic recovery. In this review, we explore the evidence for neurologic prognostication in the emergency department for patients who achieve return of spontaneous circulation after an out-of-hospital cardiac arrest.

KEYWORDS
cardiac arrest, early prognostication, emergency department, neuroprognostication, out-of-hospital cardiac arrest, prognostication, return of spontaneous circulation

1 | INTRODUCTION

Out-of-hospital cardiac arrest is one of the leading causes of morbidity and mortality in the United States. The vast majority of out-of-hospital cardiac arrest patients that achieve return of spontaneous circulation are initially managed in the emergency department (ED).[1] These post-return of spontaneous circulation patients managed in the ED should undergo cooling as part of targeted temperature management based on current evidence.[2–4] However, cooling can confound attempts at neurologic prognostication,[5–8] making early prognostic tools before targeted temperature management is initiated all the more desirable. As a result, awareness of the role, if any, for neurologic prognostication following return of spontaneous circulation in the ED is of immense importance to emergency physicians.

Among patients achieving return of spontaneous circulation, the leading cause of death is withdrawal of care due to the prognostication of a poor neurologic outcome,[9] and this often occurs within the first day of admission.[10] Neurologic prognostication following return of spontaneous circulation can occur at any moment during a patient encounter, which includes out-of-hospital, ED, or ICU settings. Ideally, one would strive to prognosticate as soon as there is certainty of the outcome to avoid additional suffering for the patient and their family, while also reducing scarce resource use. However, when the outcome is not certain, early prognostication can have dire consequences.

Elmer et al[10] sought to assess the effect of early withdrawal of care, defined as withdrawal before 72 hours due to perceived poor neurologic prognosis.[11,12] In this study, one-third of patients had early withdrawal of care with resultant death. Using a propensity-matched cohort without early withdrawal of care, these authors predicted that 16% of the early withdrawal of care patients would have survived to discharge neurologically intact if not for early withdrawal of care. These findings were replicated by May et al,[13] who found a 17%

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TABLE 1 Physical examination findings associated with poor neurologic outcomes after out-of-hospital cardiac arrest

Physical examination finding	Result indicating poor prognosis	False–positives[a] (%)	Relevant studies
Myoclonus	Any myoclonus	9–16	Bouwes et al,[19] Reynolds et al,[20] Seder et al[21]
GCS motor score	1–2 (absent or extensor only)	8–52.5	Sivaraju et al,[22] Greer et al,[24] Annborn et al,[25] Okada et al[26]
Corneal reflex	Absence bilaterally	25	Wee et al,[27] Hong et al[28]
Pupillary light reflex	Absence bilaterally	15–63	Okada et al,[26] Wee et al,[27] Hong et al,[28] Abe et al[29]

[a]False–positive refers to the examination finding indicating a poor neurologic prognosis in patient who actually made a neurologically intact recovery. GCS, Glasgow Coma Scale

incidence of early withdrawal of care for perceived poor neurologic prognosis prior to 72 hours. In this cohort, the predicted survival with a good neurologic outcome was 19% if care had not been withdrawn early. These studies emphasize the inherent danger in attempting to prognosticate neurologic outcomes too early following resuscitation from out-of-hospital cardiac arrest.

In this review, we provide an overview of the evidence for neurologic prognostication of the post-return of spontaneous circulation out-of-hospital cardiac arrest patient in the ED. We will focus on clinical examination features, imaging findings, laboratory studies, active monitoring systems, and scoring systems used to prognosticate neurologic outcomes. This review will focus on evidence for prognostication within 6 hours of return of spontaneous circulation, the time frame most relevant to the emergency physician.

2 | RATIONALE FOR AND CHALLENGES OF POST-ARREST NEUROLOGIC ASSESSMENT IN THE ED

Emergency physicians often serve as the initial point of contact for patients and their families as well as stewards in the allocation of scarce critical care resources.[14] Prognostication by an emergency physician early in a patient's course of care after an out-of-hospital cardiac arrest would be of immediate relevance to the family, avoid prolonged suffering of the patient, and often eliminate the need for costly and futile intensive care admission. However, there are many challenges in assessing the post-arrest patient in the ED. These challenges include medications such as sedation and paralytics that may confound the examination and the timing of imaging and laboratory studies which may contribute to confounding by indication.

3 | CLINICAL EXAMINATION

There are multiple clinical examination features that have been explored for their ability to prognosticate a poor outcome in a post-return of spontaneous circulation out-of-hospital cardiac arrest patient including the presence of myoclonus, extensor pain response or absent pain response, absent corneal reflexes, and absent pupillary light reflexes (Table 1).[11] These have been found to have higher sensitivity for poor outcomes, but lower specificity particularly when performed early.[11,15–17] The American Heart Association currently recommends clinical examination findings be used for prognostication only after 72 hours of normothermia.[12] Despite this, up to 25% of critical care providers surveyed indicate that they use the clinical examination for definitive prognosis before this timewindow.[18]

Studies assessing early myoclonus have found it to be associated with a poor neurologic outcome, but with poor specificity. Survival rates with a good neurologic outcome despite the presence of myoclonus within 72 hours of out-of-hospital cardiac arrest have been reported at 9%–16%.[19-22] It may be that different forms of myoclonus, such as myoclonus status epilepticus, have a worse prognosis than that of more benign forms of myoclonus such as Lance-Adams syndrome.[23] Continuous electroencephalogram (EEG) testing, discussed below, is essential to make this distinction.[23]

An extensor or absent pain response, a component of the Glasgow Coma Scale (GCS), has also been associated with poor outcomes.[22] However, 8%–36% of patients with extensor or absent pain response within 72 hours of out-of-hospital cardiac arrest have had good neurologic recovery.[22,24,25] A study evaluating GCS motor scores in the ED after return of spontaneous circulation reported that among survivors with a good neurologic outcome, 52.5% had an initial extensor or absent pain response.[26]

Evaluation of corneal reflexes affords a rapid bedside assessment of brainstem reflexes that may afford prognostic value. Bilateral absence of corneal reflexes immediately after return of spontaneous circulation has been found to be associated with worse survival and neurologic outcomes.[27,28] However, in these studies corneal reflexes were absent immediately after return of spontaneous circulation in 68% of survivors[27] and 25% of survivors with a good outcome,[28] indicating an unacceptably high false-positive rate for predicting a poor neurologic outcome.

Absent qualitative pupillary light reflex from bedside examination has also been studied as an indicator of a poor prognosis. However, the qualitative absence of pupillary light reflexes has been reported to have false–positive rate of 63%,[27] 47.5%,[29] 30%,[26] and 15%[28] when performed in the ED. Even at 24 hours, there are patients with qualitatively absent pupillary reflexes that have gone on to have good neurologic outcomes.[30]

Automated pupillometry has shown much more promise to predict survival with a good neurologic outcome (Table 2).[31–36] Automated pupillometry studies have shown improved accuracy for early prognosis, but most are unblinded and potentially limited by confirmation bias (ie, the self-fulfilling prophecy of having a test influence decisions to withdraw care). Lastly, these studies have included only

TABLE 2 Pupillometry measures associated with poor neurologic outcomes after out-of-hospital cardiac arrest

Author	Test	Timing	Measure	n	Sens (%)	Spec (%)	PPV (%)	NPV (%)
Behrends et al[31]	Pupillary light reflex	During IHCA	Absent at 5 min	30	56	100	100	41
Tamura et al[35]	Pupillary light reflex	30 min after ROSC	<6%	50	74	92	96	55
Heimburger et al[32]	Pupillary light reflex	4 h after OHCA	<9%	82	63	78	85	51
Riker et al[33]	NPi	6 h after ROSC	Value of 0	52	25	100	100	37
	Constriction velocity		<0.23 mm/s	52	47	100	100	46
Suys et al[34]	Pupillary light reflex	16 h after ROSC	<13%	50	67	91	90	70
Oddo et al[36]	NPi	"day 1" after OHCA	≤2	450	22	100	100	47

IHCA, in-hospital cardiac arrest; OHCA, out-of-hospital cardiac arrest; NPi, neurological pupil index; ROSC, return of spontaneous circulation.

TABLE 3 Brain CT abnormalities within 6 hours after ROSC associated with poor neurologic outcome after out-of-hospital cardiac arrest

Author	Timing	CT abnormality	N	Sens (%)	Spec (%)	PPV (%)	NPV (%)
Kim et al[43]	within 1 h after ROSC	avg. GWR <1.14	51	13	100	100	44.7
Lee et al[44]	within 1 h after ROSC	Putamen/corpus callosum <1.17	186	53	100	NR	NR
Choi et al[40]	avg. 4 h (max 24 h) after ROSC	avg. GWR <1.22	28	63	100	100	56
Metter et al[46]	median 4 h (max 24 h) after ROSC	avg. GWR <1.20	240	36	98	97	46
Inamasu et al[41]	within 1 h after ROSC	Loss of boundary at basal ganglia	75	81	92	98	48
Yamamura et al[47]	within 2 h	Cerebral cortex WM difference in HU <5.5	58	63	100	100	86
Lee et al[45]	1 h after ROSC	avg. GWR <1.23	30	76	100	100	45
Chae et al[39]	6 h after ROSC	avg. GWR <1.14	119	20	100	100	43.3
Jeon et al[42]	Median 90 min (max 6 h)	avg. GWR <1.21	39	76	100	100	46.2

All studies are retrospective, single-center studies. GWR, gray–weight matter ratio; HU, Hounsfield unit; NR, not reported, data unavailable to calculate; ROSC, return of spontaneous circulation.

a small number of patients with false–positive rates ranging from 0%–22%.

4 | IMAGING STUDIES

4.1 | Computed tomography

Computed tomography (CT) scans have been studied with a particular focus on the loss of gray–white matter ratio attenuation as a potential predictor for poor neurologic outcomes. Loss of gray–white matter ratio is indicative of cerebral edema and felt to correlate with hypoxic ischemic changes in different areas of the brain. In a 2018 meta-analysis that included 1150 patients from retrospective studies, the pooled sensitivity and specificity for loss of gray–white matter ratio at predicting a poor neurologic outcome was 29% and 97%, respectively.[37] Similar findings were reported in a 2019 meta-analysis of 20 studies and 2327 patients where the sensitivity and specificity of loss of gray–white matter ratio on CT was 44% and 97%, respectively.[38] However, both of these meta-analyses included patients receiving CT scans up to 48 hours and 7 days, respectively.

There are 10 published studies evaluating the ability of early CT (within 6 hours) to predict outcomes in out-of-hospital cardiac arrest patients. Nine of these studies reported specificities, and all were retrospective single-center studies involving a total of 826 patients (Table 3).[39–47] The majority of studies chose a gray–white matter ratio cutoff that would afford 100% specificity, and the resultant sensitivity ranged from 13%–81%. These studies used different cutoffs of gray–white matter ratio ranging from 1.14–1.23, and some included patients who did not receive targeted temperature management. Additionally the methods of measuring gray–white matter ratio, including location and degree of automation, varied significantly. Furthermore, the indications for performing the CT scan were not universally reported. Often, a CT scan is ordered to assess for injuries related to trauma from a fall after an arrest or to assess for alternative etiologies of arrest such as spontaneous intracranial hemorrhage. A more recent prospective, multi-center study evaluated 512 patients receiving CT within 2 hours of return of spontaneous circulation after out-of-hospital cardiac arrest and found no correlation between gray–white matter ratio and neurologic outcome at 6 months.[28] Given the higher quality of this recent prospective study, the validity of earlier retrospective CT studies and meta-analysis must be brought into question.

4.2 | Magnetic resonance imaging

Magnetic resonance imaging (MRI) has also been studied as a means to provide earlier prognostication after out-of-hospital cardiac arrest.

Ischemic injury on MRI can be measured by abnormalities in the apparent diffuse coefficient or the presence of high signal intensity on diffusion weighted MRI (DW-MRI). MRI has greater soft tissue resolution than CT and may afford a more robust evaluation of hypoxic ischemic injury. In a systematic review of DW-MRI to predict neurologic outcome after cardiac arrest performed up to 5 days after return of spontaneous circulation, the pooled sensitivity and specificity were 75% and 91% for non-traumatic out-of-hospital cardiac arrest patients and 66% and 95% for targeted temperature management-treated patients, respectively.[38] Three studies have assessed MRI as a predictive tool when performed within 6 hours after return of spontaneous circulation and before initiation of targeted temperature management. The first study used MRI at 2 hours after return of spontaneous circulation to predict the outcomes of 10 witnessed out-of-hospital cardiac arrest patients.[48] These authors found no correlation between initial MRI and outcome or ischemic lesions seen on subsequent 24- or 96-hour MRIs. However, in this study 9 of the 10 patients had a good neurologic outcome, suggesting that this was an unusual cohort of out-of-hospital cardiac arrest patients.[48] This study used the apparent diffuse coefficient for evaluation of ischemia, whereas a subsequent study[49] of 19 out-of-hospital cardiac arrest patients evaluated high signal intensity in 21 brain regions on DW-MRI at 6 hours after return of spontaneous circulation as a predictor of poor neurologic outcome. In patients with high signal intensity, the sensitivity was 90% and specificity 100% for poor neurologic outcomes.[49] In a follow-up study by the same group involving 47 patients receiving MRI within 6 hours, the sensitivity was 75% and specificity 100% for poor neurologic outcomes.[42] Additional studies are needed to assess the feasibility of early MRI after return of spontaneous circulation for neurologic prognostication and to determine if its specificity persists in a larger, generalized patient population while maintaining reasonable sensitivity prior to the initiation of targeted temperature management.

4.3 | Ultrasound

More recently, ultrasound has been studied as an adjunct to the clinic examination through measurement of the optic nerve sheath diameter as a correlate for neurologic outcome. A larger optic nerve diameter may be indicative of increased intracranial pressure from cerebral edema and thus a worse neurologic outcome. A meta-analysis of 3 studies (102 patients) evaluating optic nerve sheath diameter measured by ultrasound as a predictor of poor neurologic outcomes after out-of-hospital cardiac arrest reported a pooled sensitivity and specificity of 77% and 98%, respectively.[50] However, this study did not include ultrasound studies conducted within a 6-hour window from return of spontaneous circulation or in the ED. In a subsequent study evaluating optic nerve sheath diameter in 36 patients by 1 operator immediately post-return of spontaneous circulation and at 24-, 48-, and 72-hour intervals, there was no correlation with measurements obtained immediately post-return of spontaneous circulation and patient outcome.[51] At 24 hours, the authors found that an optic nerve sheath diameter over 4.9 mm had a sensitivity of 83.3% and a specificity of 94.4% and a PPV of 93.7% for predicting a poor neurologic outcome.

5 | LABORATORY TESTING

There are a multitude of common and special laboratory tests that have been used to assist in prognostication after out-of-hospital cardiac arrest. One of the most readily available blood tests in the ED is the venous or arterial blood gas measurement, which affords rapid point-of-care assessment of a patient's pH. Studies that have evaluated the ability of initial arterial pH (within 2 hours of return of spontaneous circulation) to predict outcome have found no significant association between a pH above 7.1 and neurologic recovery.[52] Although a pH equal to or below 7 had 4.5 greater odds for a poor neurologic outcome, there were some survivors discharged neurologically intact with initial pH below 7, making pH alone an imperfect prognostic tool.

Lactate, procalcitonin, troponin, d-dimer, and C-reactive protein are other routinely available laboratory tests that have been studied as prognostic tests due to their associations with worse patient outcomes after out-of-hospital cardiac arrest.[25,53,54] However, despite these associations, none of these markers have been found to be reliable predictors of a poor prognosis with no false–positives (Table 4). Rather, they are more commonly used as components of scoring systems, discussed below, to predict outcomes for out-of-hospital cardiac arrest patients.

Advanced neurologic serum biomarkers such as neuron-specific enolase (NSE), neurofilament light chain (NFL), and S100-B protein have also been studied in an effort to predict outcomes for cardiac arrest patients. NSE is released after neuronal injury, NFL after axonal injury, and S100-B after astroglial and Schwann cell injury. Their presence and levels are thought to reflect the degree of neurologic injury following out-of-hospital cardiac arrest, and although these assays are not routinely available in the ED setting, they could be rapidly commercialized if proven useful in prognosis (Table 5).

In a study assessing NSE elevation at the time of ICU admission using a cutoff level of 33 ng/mL, the authors reported a specificity of 60% with a sensitivity of 64%.[55] Although this same cutoff value had 91% specificity and 60% sensitivity at day 5, its value as a predictor of poor neurological outcome immediately post-return of spontaneous circulation appears poor, in part because NSE levels do not reach peak concentrations until at least 24 hours after injury. This is consistent with the findings from a recent study that showed that NSE measured immediately after return of spontaneous circulation was not significantly different ($P = 0.854$) between those with a poor compared to good neurologic outcome and that a high cutoff value of 42.2 ng/mL was required for a specificity of 94%, which decreased the sensitivity to 17%.[54]

NFL similarly shows promise as a predictor of poor neurologic outcome after admission for out-of-hospital cardiac arrest patients and has been shown to have a higher sensitivity and specificity than NSE or S100-B at 24 hours.[56] However, measurements of the NFL within 6 hours after out-of-hospital cardiac arrest have had mixed results,

TABLE 4 Laboratory test abnormalities associated with poor neurologic outcome after out-of-hospital cardiac arrest

Test	Isenschmid et al[53]	Park et al[54]	Annborn et al[25]
Troponin	OR 2.12 (1.48–3.06)[a]	NS, Sens. 87%, Spec. 42% (cutoff 0.78 ng/mL)	Not evaluated
Pro-BNP	NS[a]	NS, Sens. 23%, Spec. 88% (cutoff 1229 pg/mL)	Not evaluated
D-dimer	Not evaluated	NS, Sens. 47%, Spec. 70% (cutoff 13.7 mg/L FEU)	Not evaluated
Procalcitonin	OR 2.48 (1.83–3.38)[a]	NS, Sens. 100%, Spec. 6% (cutoff 6.05 ng/mL)	$P < 0.01$ (6 h), 12 h Sens. 100%, Spec. 15% (cutoff 10 ng/mL)
Lactate	OR 12.58 (5.23–29.56)[a]	NS, Sens. 60%, Spec. 61% (cutoff 4.32 mmol/L)	Not evaluated
CRP	OR 1.66 (1.11–2.48)[a]	Not evaluated	NS at 2 h and 6 h[b]
Urea	NS[a]	Not evaluated	Not evaluated
Fibrinogen	Not evaluated	NS, Sens. 100% Spec. 9% (cutoff 128.2 mg/mL)	Not evaluated

NS, not significant; CRP = c-reactive protein

For Park et al,[54] optimal cutoffs calculated per Euclidean method, for troponin Isenschmid et al[53] used high-sensitivity troponin T whereas Park et al used Trop-I.

[a]Per authors, the OR corresponds to any 10-fold increase in log transformed blood marker levels.

[b]Because no significance was found between CRP and neurologic outcome, a cutoff value was not reported.

TABLE 5 Biomarkers of neurologic injury associated with poor neurologic outcome after out-of-hospital cardiac arrest

Author	Test	Timing	Measure	n	Sens (%)	Spec (%)	PPV (%)	NPV (%)
Luescher et al[55]	NSE	At ICU admission	33 ng/mL or higher	336	64	60	68	56
Park et al[54]	NSE	Immediately after ROSC	42.2 ng/mL	102	17	94	85	42
Moseby-Knappe et al[56]	NFL	24 h	>641 pg/mL	717	64	99	98	73
Rana et al[57]	NFL	<2 h	>323 pg/mL	85	79	100	100	94
Rundgren et al[58]	NFL	Post-ROSC, 2 h, 6 h	Elevated NFL	90	N/A[a]	N/A[a]	N/A[a]	N/A[a]
Park et al[54]	S100-B	Immediately after ROSC	1.93 μg/L	102	55	76	80	52

NFL, neurofilament light-chain; NSE, neuron specific enolase; ROSC, return of spontaneous circulation.

[a]The study could not identify clinically meaningful cut-off levels separating good and poor outcomes.

with 1 study finding 100% specificity at a cutoff of 323 pg/mL with sensitivity of 79% whereas another reported that no clinically meaningful cut-off could be identified and that there were no significant differences in post-return of spontaneous circulation NFL levels among poor outcome and good outcome patients.[57,58] S100-B when measured immediately after return of spontaneous circulation is significantly higher in those with a poor neurologic outcome ($P < 0.001$), but has a specificity of only 76% with a sensitivity of 55%, indicating a still unacceptably high false–positive rate.[54]

6 | ACTIVE NEUROLOGIC MONITORING

6.1 | Near-infrared spectroscopy

Near-infrared spectroscopy (NIRS) can be used to assess regional cerebral oxygen saturation (rSO2). This is a non-invasive strategy that can be used both pre- and post-return of spontaneous circulation in the out-of-hospital cardiac arrest patient. Although initial studies evaluating rSO2 beginning immediately post-return of spontaneous circulation in out-of-hospital cardiac arrest patients found no survivors with favorable neurologic status when rSO2 was <40% (n = 89)[59] or <30% (n = 43),[60] subsequent studies (n = 25, n = 118)[61,62] reported no association between any NIRS rSO2 value immediately after ICU admission and neurologic outcomes in out-of-hospital cardiac arrest patients receiving targeted temperature management. Further large, prospective multi-center studies are needed to understand the value of NIRS rSO2 to predicting neurological outcomes prior to and after initiation of targeted temperature management.

6.2 | EEG

EEG is a monitoring tool that can be used to directly evaluate brain activity and assess for neurologic damage in the comatose post-return of spontaneous circulation patient. However, most studies on the ability of an EEG to predict a poor neurologic outcome have been conducted much later during the hospital stay and findings have often been limited by signal interference in patients undergoing targeted temperature management. A study evaluating patients 77 hours after return of spontaneous circulation reported a specificity of 100% and a sensitivity of 50% for background suppression and burst suppression in predicting a poor neurologic outcome.[63] Using these same measures, another study evaluated EEGs ability to predict poor outcomes at 24 hours

TABLE 6 Scoring systems to predict poor neurologic outcome within 6 hours of out-of-hospital cardiac arrest

Author	Test	Timing	Poor predictor	n	Sens (%)	Spec (%)	PPV (%)	NPV (%)
Adrie et al[66]	OHCA[a]	At ICU admission	Score >32.5	210	80	85	94	56
Maupain et al[67]	CAHP[b]	At ICU admission	Score >200	434	46	96	96	48
Martinell et al[68]	TTM-risk score[c]	At ICU admission	Score > 16	933	41	96	91	59
Kiehl et al[69]	C-GRApH[d]	After ROSC	Score ≥ 4	344	30	97	98	27
Shih et al[70]	SWAP[e]	At ED arrival	Score = 4	859	33	100	100	3

CAHP, Cardiac Arrest Hospital Prognosis; OHCA, out-of-hospital cardiac arrest; ROSC, return of spontaneous circulation; SWAP, shockable rhythm-witness-age-pH; TTM, targeted temperature management

Above test characteristics based on validation cohorts. SWAP score based on those with ongoing CPR on ED arrival.

Scores included the following constituent variables:

[a]initial rhythm, no-flow interval, low-flow interval, serum creatinine, arterial lactate.

[b]age, initial rhythm, no-flow interval, low-flow interval, arrest location, total epinephrine dosing, arterial pH.

[c]age, initial rhythm, no-flow interval, low-flow interval, arrest location, total epinephrine dosing, absence of corneal and pupillary reflexes, GCS motor response of 1, arterial pH, arterial pCO_2.

[d]age, initial rhythm, initial pH, coronary artery disease history, initial glucose value.

[e]age, initial rhythm, witnessed status, initial pH.

(100% specificity, 29% sensitivity) and 12 hours (88% specificity, 51% sensitivity).[64] In a study assessing post-return of spontaneous circulation automated EEG readings for bispectral index (BIS) and suppression ratio (SR) at a mean of 4.6 hours after return of spontaneous circulation, the authors reported 94% specificity and 86% sensitivity for a BIS cutoff of 22% and 93% specificity and 84% sensitivity for a SR cutoff of 48. Studies evaluated BIS and SR at 4 hours after cardiopulmonary resuscitation (CPR) initiation found 89.5% specificity and 85.7% sensitivity for poor neurologic outcomes.[65] Despite these high specificities the number of false positive predictions of poor neurologic outcome based on early EEG-based tests remains unacceptably high.

7 | SCORING SYSTEMS

In an attempt to produce better post-return of spontaneous circulation neurologic prognostication, several efforts have combined clinical features, physical findings, and diagnostic test results to predict neurologic outcome (Table 6). These systems combine arrest characteristics (ie, witnessed out-of-hospital cardiac arrest, public location, etc) with readily available data in the ED to provide an estimate for poor neurologic recovery within 6 hours of return of spontaneous circulation.

The out-of-hospital cardiac arrest score was the first of these scoring systems and combined variables including the initial rhythm, no-flow interval, low-flow interval, serum creatinine, and arterial lactate to produce a score.[66] No-flow interval refers to the time from arrest to the initiation of CPR whereas low-flow interval is the time of active CPR until return of spontaneous circulation. The out-of-hospital cardiac arrest score was found to only be 77% specific for poor outcomes in the derivation cohort and 85% in the validation cohort. In an attempt to improve on the out-of-hospital cardiac arrest score, the Cardiac Arrest Hospital Prognosis score was developed.[67] This score combines age, initial rhythm, no-flow time, low-flow time, arrest location (defined as home-setting), total epinephrine dosage, and arterial pH. The defined high-risk score (>200) had 98%, 96%, and 100% specificity for poor neurologic outcome in the development, prospective validation, and retrospective validation cohorts, respectively. However, subsequent studies evaluating the Cardiac Arrest Hospital Prognosis score on other cohorts of out-of-hospital cardiac arrest patients have reported lower specificities of 82%–83%.[68]

Two scoring systems were subsequently developed to better determine the likelihood for poor neurological outcome for patients at the time of ICU admission who were subsequently treated with targeted temperature management. The first was the targeted temperature management-risk score that combined age, arrest location (home vs elsewhere), non-shockable initial rhythm, no-flow duration, low-flow duration, epinephrine administration, absence of corneal and pupillary reflexes, GCS motor response of 1, pH (point values −1 to 3 based on pH), and lower partial pressure of carbon dioxide in arterial blood (3 points if <4.5 kPa).[68] Using these parameters, a score of over 16 had 96% specificity for a poor neurologic outcome. The second score was the C-GRApH score, which combined history of known coronary artery disease, initial glucose ≥200 mg/dL, non-shockable initial rhythm, age over 45, and initial pH ≤ 7.0.[69] A score of 4 or greater had a specificity of 97% for poor outcomes. Although better than the out-of-hospital cardiac arrest and Cardiac Arrest Hospital Prognosis scores, these scoring systems still have false–positive rates of 3%–4%.

To produce a simpler score specific for the ED, the shockable rhythm-witness-age-pH score was created.[70] This score was derived from a cohort of 852 out-of-hospital cardiac arrest patients using 4 variables: shockable initial rhythm, witnessed arrest status, age, and either arterial or venous pH. A score of 4 points (non-shockable initial rhythm, unwitnessed arrest, age >60, and pH ≤7) was found to have 97% specificity in their derivation cohort and 100% specificity in their validation cohort for poor neurologic outcome. Only patients who had not achieved field return of spontaneous circulation on ED arrival were included in the study, suggesting that a patient meeting their definition of a poor prognosis (shockable rhythm-witness-age-pH score of 4) would have had an unwitnessed arrest with initial non-shockable rhythm and no return of spontaneous circulation prior to ED arrival.

Those patients would already meet established out-of-hospital termination of resuscitation guidelines from emergency medicine services research, which have been shown to have a positive predictive value for non-survival of 99.5% in prospective validation studies.[71–73]

Balan et al[74] created a similar simple scoring system to shockable rhythm-witness-age-pH, the cardiac arrest survival score (CASS), to predict in-hospital mortality, not neurologic outcome, after out-of-hospital cardiac arrest. The score combined age (>75, 3 points), unwitnessed arrest (4 points), arrest at home (2.5 points), no bystander CPR (2.5 points), and non-shockable initial rhythm (8 points) to produce a linear score associated with in-hospital mortality with an area under the curve of 0.717 and 0.708 for the derivation and validation cohorts, respectively. However, this was not sufficiently specific as there was still 10% survival for those with a maximum CASS score of 20.

8 | CLINICAL IMPLICATIONS AND FUTURE DIRECTIONS

Although there are many features of the physical examination, imaging studies, and laboratory workup that can suggest a poor prognosis, there is insufficient evidence at this time to support early withdrawal of care based on prognostic testing available in the ED or within 6 hours of return of spontaneous circulation. Clinicians should instead focus on aggressive care for the post-arrest patient including initiating targeted temperature management and optimizing hemodynamic support. Should families inquire about prognosis, it is reasonable to inform them of the likely, but not certain, poor prognosis based on the tools discussed in this review.

There is great potential value in early prognostication of neurologic outcome after return of spontaneous circulation in the post-arrest patient. Such a tool would significantly reduce family suffering and unnecessary and expensive ICU care. To reach this point, future studies should focus on objective, reproducible findings on physical examination in conjunction with laboratory and imaging studies while factoring in event characteristics such as initial rhythm, witnessed status and presence of bystander CPR. For example, studies on pupillometry indicate it is less subjective and more accurate than physical examination at determining pupil response and future studies should attempt to generalize its use in predicting poor outcomes after out-of-hospital cardiac arrest.

Future studies on CT imaging need to establish a predetermined gray–white matter ratio cutoff, rather than choosing a gray–white matter ratio, retrospectively, that results in 100% specificity. This will afford more accurate prospective validation of CT for prognostication in a reproducible way. Although MRI is a promising prognostic modality in a set of single-center studies at 6 hours, future studies need to externally validate these findings and assess the safety and feasibility of performing early MRI.

Although the current scoring systems (Table 6) combine many variables, they do not incorporate advanced imaging, pupillometry data, or novel biomarker assays, all of which represent potential areas of exploration for future studies aimed at improving the specificity of these scores. It is most likely that a combination of the above modalities will be needed to afford 100% specificity. Finally, any future study on neurologic prognostication should be blinded and use a cohort where early withdrawal of care was actively discouraged so as to produce the most accurate prognostic tool.

9 | CONCLUSIONS

For the out-of-hospital cardiac arrest patient with return of spontaneous circulation in the ED there are no clinical examination findings, imaging results, laboratory studies, monitoring tests, or scoring systems that predict poor neurologic outcomes with enough statistical certainty to inform withdrawal of care discussions or preclude the need for targeted temperature management and ICU admission. Based on the available data, physicians should avoid attempts at early withdrawal of care in the ED.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

JL reviewed the literature, wrote the manuscript, compiled edits, and takes final responsibility for the manuscript; MK and MD edited the manuscript and contributed to the literature review.

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