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Clinical paper

Distinct predictive values of current neuroprognostic guidelines in post-cardiac arrest patients

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Abstract

Purpose: To assess the performance of neuroprognostic guidelines proposed by the American Academy of Neurology (AAN), European Resuscitation Council/European Society of Intensive Care Medicine (ERC/ESICM), and American Heart Association (AHA) in predicting outcomes of patients who remain unconscious after cardiac arrest.

Methods: We retrospectively identified a cohort of unconscious post-cardiac arrest patients at a single tertiary care centre from 2011 to 2017 and reviewed hospital records for clinical, radiographic, electrophysiologic, and biochemical findings. Outcomes at discharge and 6 months post-arrest were abstracted and dichotomized as good (Cerebral Performance Category (CPC) scores of 1–2) versus poor (CPC 3–5). Outcomes predicted by current guidelines were compared to actual outcomes, with false positive rate (FPR) used as a measure of predictive value.

Results: Of 226 patients, 36% survived to discharge, including 24 with good outcomes; 52% had withdrawal of life-sustaining therapies (WLST) during hospitalization. The AAN guideline yielded discharge and 6-month FPR of 8% and 15%, respectively. In contrast, the ERC/ESICM had a FPR of 0% at both discharge and 6 months. The AHA predictors had variable specificities, with diffuse hypoxic-ischaemic injury on MRI performing especially poorly (FPR 12%) at both discharge and 6 months.

Conclusions: Though each guideline had components that performed well, only the ERC/ESICM guideline yielded a 0% FPR. Amongst the AAN and AHA guidelines, false positives emerged more readily at 6 months, reflective of continuing recovery after discharge, even in a cohort inevitably biased by WLST. Further assessment of predictive modalities is needed to improve neuroprognostic accuracy.

Keywords: Cardiac arrest, Neuroprognostication, Self-fulfilling prophecy, Hypoxic-ischaemic encephalopathy, Post-cardiac arrest syndrome, Outcomes assessment, Heart arrest

Introduction

Neurologic prognosis is frequently uncertain in individuals who are unconscious following cardiac arrest, as the degree of hypoxic-ischaemic brain injury may be difficult to assess early on. For those with return of spontaneous circulation (ROSC) after out-of-hospital cardiac arrest, between 50% and 90% fail to survive to hospital discharge.[1,2] Regardless of the aetiology of arrest, the majority of comatose post-arrest patients die after withdrawal of life-sustaining therapies (WLST) due to a perceived poor neurologic prognosis.[3–5] During neuroprognostication, clinicians must balance two competing goals: 1) avoiding premature WLST in patients who may achieve a good neurologic outcome, and 2) avoiding prolonging care in patients destined for a poor outcome. Adopting a multimodal approach to neuroprognostication is recommended,[6–11] as no individual modality is infallible.

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In the 2006 American Academy of Neurology (AAN) practice parameters for cardiac arrest survivors,[12] myoclonic status epilepticus (MSE) on post-arrest day 1, bilaterally absent N20 somatosensory evoked potentials (SSEP), elevated serum neuron specific enolase (NSE) levels, and absent pupillary or corneal reflexes with extensor or absent motor response on day 3 are regarded as poor outcome predictors. This algorithm, however, is derived from studies pre-dating the widespread use of targeted temperature management (TTM), which alters cellular metabolism[13] and delays clearance of sedatives and paralytics,[14–16] thus also delaying clinical signs of recovery.[17–20]

In contrast, the 2014 European Resuscitation Council/European Society of Intensive Care Medicine (ERC/ESICM) guideline[21] comprises recent data on TTM-treated patients, with acknowledgement of varying levels of prediction confidence, and reaffirm the complete abolishment of pupillary and corneal reflexes and N20 potentials as robust poor outcome predictors. The 2015 American Heart Association (AHA) guideline[22] assesses current prognostic modalities separately, including their timing in relationship to TTM, and establishes the absence of pupillary reflexes at 72 h in TTM-treated patients as the only poor prognostic parameter with Class I evidence.

In an era of variable management strategies and evolving neuroprognostic tools, it is imperative that prognostic strategies are accurate. Measurements of accuracy, however, are inherently confounded by the self-fulfilling prophecy from WLST, in which treating physicians are not blinded to the results of a prognostic assessment and consequently use them to inform care decisions. The purpose of this study is to ascertain the neuroprognostic performance of the AAN, ERC/ESICM, and AHA guidelines when applied to a real-world cohort of patients. We hypothesized that the guidelines overestimate their predictive value, such that actual false positive rates (FPR) at both hospital discharge and 6 months are higher than reported.

Methods

Sample selection

The study was approved by the Yale University Human Investigation Committee (HIC# 2000021220), and the need for informed consent was waived. The cohort was retrospectively identified by querying the electronic medical record (EMR) for patients age 18 years or older with a cardiac arrest diagnosis code (ICD-9-427.5/ICD-10-I46.9) between January 2011 and June 2017. Additional inclusion criteria included successful resuscitation and unconsciousness for at least 24 h after ROSC. Patients who died or had WLST within the first 24 h were excluded (Fig. 1).

Data collection

Data abstracted from the EMR included demographics, arrest location, non-perfusing rhythms, and details of TTM when applicable. Neuroprognostic variables included the clinical examination (pupillary light reflex, corneal reflex, motor response to pain, and post-anoxic myoclonus), EEG, SSEP, head CT, brain MRI, and serum NSE levels. Electrophysiologic and radiologic data were abstracted from final reports for these studies. MSE was discerned by either EEG report or EMR documentation by a neurologist. All results were retrospectively collected

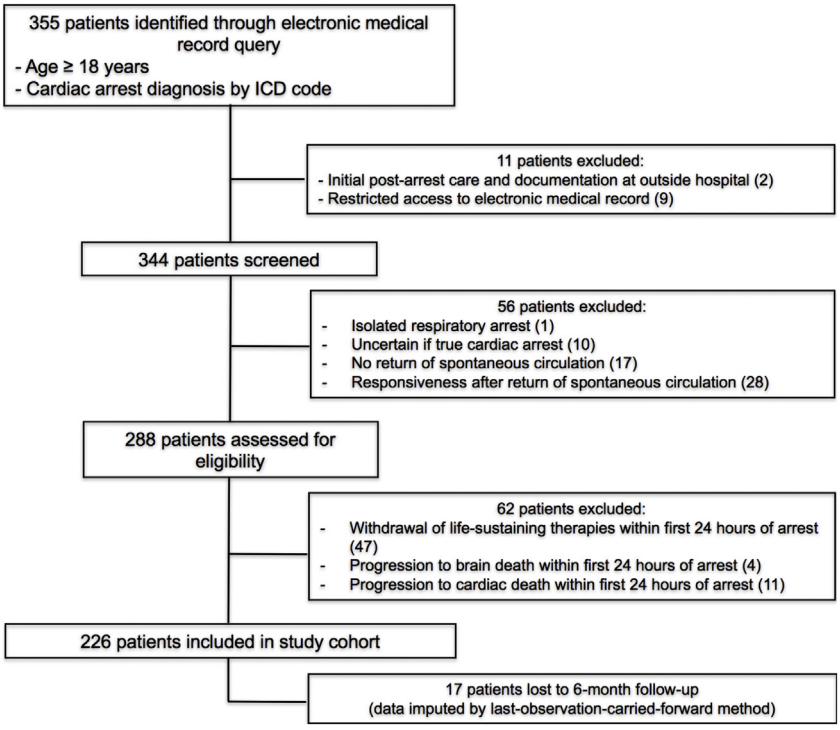

Fig. 1 – Patient selection and follow-up.

Patient selection and follow-up. Patients were considered lost to follow-up when there was no clinical documentation in the electronic medical record at 6-months post-arrest. ICD = International Statistical Classification of Diseases and Related Health Problems.

at the time points specified by each guideline, including with respect to time of rewarming after TTM when indicated, with the exception of the AHA recommendation of head CT within the first two hours after ROSC, which was extended to the first 24 h to account for imprecise time of ROSC in a large subset of patients. As the AAN guideline does not distinguish between TTM-treated and non-TTM-treated patients, all AAN time points were based on time of ROSC.

Outcomes were assessed using the Cerebral Performance Category (CPC) scale. Scores were assigned retrospectively based on EMR documentation of cognitive and functional status, including documentation by rehabilitation specialists, at both discharge and 6 months. For 17 patients for whom no 6-month follow-up was documented, the discharge outcome score was carried forward. CPC scores were dichotomized as "good" outcome (CPC 1–2) versus "poor" outcome (CPC 3–5). All CPC scores in survivors were adjudicated by a board-certified neurointensivist (CBM) blinded to details of the case.

Statistical analysis

Statistical analyses were performed using GraphPad Prism version 7.0a for Mac OS X (GraphPad Software, La Jolla California USA, www.graphpad.com). Categorical variables are presented as counts and percentages, and continuous variables as mean and standard deviation (SD) or, for non-normally distributed data, median and interquartile range (IQR). Fisher's exact test was used to determine statistical significance of contingency tables, with an alpha level of 0.05. For FPR, the 95% confidence interval (CI) was approximated via the Wilson–Brown method.

Data availability

Anonymized data will be shared with any qualified investigator upon request.

Results

Demographic data

A total of 226 patients met the study criteria. The population was predominantly male (55%) and non-Hispanic white (58%), with an average age of 58 years (Table 1). Sixty-two percent suffered an out-of-hospital arrest. Non-perfusing rhythms included pulseless electrical activity (50%), asystole (23%), ventricular fibrillation or ventricular tachycardia (20%), and unknown rhythm (7%). Fifty-seven percent of patients underwent TTM, and 45 (30%) had a targeted temperature of 36 °C.

Outcomes at discharge and 6 months

WLST prior to hospital discharge occurred in 118 patients (52%) (Table 1). The median WLST time was post-arrest day 6 (IQR 4–12), although 25 (11%) had WLST on days 2–3. Twenty-six patients (12%) progressed to brain death during hospitalization (median day 4; IQR 2–6), and seven (3%) progressed to cardiac death (median day 4; IQR 2–29) due to recurrent cardiac arrest and/or progressive cardiovascular collapse. Eighty-one patients (36%) survived to discharge, including 24 (11%) with a good outcome.

Table 1 – Patients' characteristics and neuroprognostic studies.

	Total N = 226
Female, N (%)	102 (45)
Age, years, mean (SD)	58 (17)
Race/ethnicity, N (%)	
Non-Hispanic white	133 (59)
Non-Hispanic black	56 (25)
Hispanic	28 (12)
Other/unknown	9 (4)
Arrest location, N (%)	
Out of hospital	139 (62)
Emergency department	19 (8)
In hospital	68 (30)
Arrest rhythm, N (%)	
VF/VT	45 (20)
Pulseless electrical activity	112 (50)
Asystole	53 (23)
Unknown	16 (7)
TTM, N (%)	136 (60)
Target temperature 32–34 °C	95 (70)
Target temperature 36 °C	41 (30)
Neuroprognostic study, N (%)	
EEG	197 (87)
SSEP, days 1–5	43 (19)
NSE, days 1–3	45 (20)
Head CT, ≤24h	180 (80)
Brain MRI, days 2–6	96 (42)
Survival to discharge, N (%)	81 (36)
CPC score 1	15 (7)
CPC score 2	9 (4)
CPC score 3	42 (19)
CPC score 4	15 (7)
Hospital progression to brain death, N (%)	26 (12)
Days to brain death, median (IQR)	4 (2–6)
Hospital progression to cardiac death, N (%)	7 (3)
Days to cardiac death, median (IQR)	4 (2–29)
WLST, N (%)	118 (52)
WLST day, median (IQR)	6 (4–12)
6-month outcome, N (%)	
CPC score 1	21 (10)
CPC score 2	12 (5)
CPC score 3	29 (13)
CPC score 4	7 (3)
CPC score 5	157 (69)

Abbreviations: VF/VT = ventricular fibrillation/ventricular tachycardia; TTM = targeted temperature management; SSEP = somatosensory evoked potential; NSE = neuron specific enolase; CPC = Cerebral Performance Category; IQR = interquartile range; WLST = withdrawal of life-sustaining therapies.

Twelve patients died between discharge and 6 months, for a total of 157 patients (69%) with CPC 5 at 6 months. Twelve additional patients improved to a good outcome, for a total of 33 patients (41% of discharge survivors) with a good 6-month

outcome. Four patients worsened after discharge from a CPC score of 1–3 (3 patients) or 2–3.

Rates of neuroprognostic assessments

Continuous EEG was obtained in 87% of patients (Table 1). Eighty percent of patients had a head CT within 24 h of arrest, and 53% had a brain MRI during hospitalization. Seven percent underwent SSEP between days 1–3, and another 13% on days 4-5. Twenty percent had serum NSE measured between days 1–3 (Fig. 2).

Predictive value of the AAN guideline

Based on the AAN guideline, 113 patients (50%) were predicted to have a poor neurologic outcome (Table 2). Of these, 94 (83%) did not survive to discharge, including 75 (66%) with WLST. Of the 19 survivors, two had a good discharge outcome, for an overall FPR of 8% (95% CI, 1–26%). One had been predicted to do poorly due to absent motor response and corneal reflexes on post-arrest day 3, while the other had an NSE level greater than 150.0 mcg/L on day 2; both were treated with TTM.

At 6 months, the FPR increased to 15% (95% CI, 7–31%), reflecting three patients who improved following discharge. Two had absent pupillary reflexes with absent motor response on day 3, while the other had elevated NSE levels on days 1 and 2 (37.3 and 45.2 mcg/L, respectively). All three patients were treated with TTM.

Predictive value of the ERC/ESICM guideline

On post-arrest days 3–5, for patients with an absent or extensor motor response to pain, the ERC/ESICM guideline recommends two robust predictors of "very likely" poor outcome: absent N20 SSEP and/or absence of both pupillary and corneal reflexes. Based on these criteria, the FPR was 0% at both discharge (95% CI, 0–14%) and 6 months (95% CI, 0–10%) (Table 3).

Of 207 survivors to day three, 33 (16%) were predicted to have a poor outcome based on the aforementioned criteria. All either died prior to discharge (94%), including 22 (69%) due to WLST, or were discharged with a CPC score of 4 (6%). Of 189 survivors to day four, 32 (17%) fulfilled above criteria for poor outcome; all had an in-hospital death, 23 (72%) due to WLST. On day five, 26 of 169 patients (15%) fulfilled criteria for poor outcome. Twenty-four (92%) died before discharge, either secondary to WLST (17 patients) or by progression to brain death (7 patients). Of the survivors, one was discharged with CPC 4 and the other with CPC 3; none improved at 6 months.

The ERC/ESICM guideline also predicts "likely" poor outcome with $\geq$2 of the following: 1) MSE within 48 h of ROSC, 2) high NSE at 48–72 h, 3) unreactive burst-suppression or status epilepticus, and 4) diffuse hypoxic-ischaemic injury on CT (within 24 h) or MRI (days 2–5). As "high NSE" is not defined, the AAN threshold of 33 mcg/L was used, although the guideline acknowledges the varying sensitivity and specificity of different cut-offs according to the type of assay used and the sample timing. All 48 patients meeting multimodal criteria had a poor discharge outcome. Forty-three (90%) did not survive to discharge, with 36 having WLST, and no survivors showed improvement at 6 months, for a FPR of 0% (Table 3).

Predictive value of the AHA guideline

Absent pupillary reflexes on days 3–4 after ROSC yielded no false positives at discharge (Table 4). However, two patients with absent pupillary reflexes on day 3 achieved a good 6-month outcome, for a FPR of 6% (95% CI, 1–20%). These patients regained pupillary reflexes on days 4 and 5, respectively; neither underwent TTM nor had other AHA-specified poor prognostic parameters.

MSE within 72 h, unreactive EEG, status epilepticus, and persistent burst-suppression all demonstrated 0% FPR at discharge. At 6 months, only MSE yielded a false positive, for a FPR of 3% (95% CI, 0–15%).

Neither absent N20 potentials on days 1–3 nor NSE above 33 mcg/L on days 2–3 yielded false positives at discharge, but the incidences of these findings were low and not statistically significant. At 6 months, elevated NSE generated one false positive for a FPR of 25% (95% CI, 1–70%). This patient, who had up-trending NSE levels on days 1 and 2 from 37.3 mcg/L to 45.2 mcg/L, improved from CPC 3 to 2. One study[17] suggests an NSE threshold of 78.9 mcg/L after TTM, and when applied to this cohort, the results yielded no false positives.

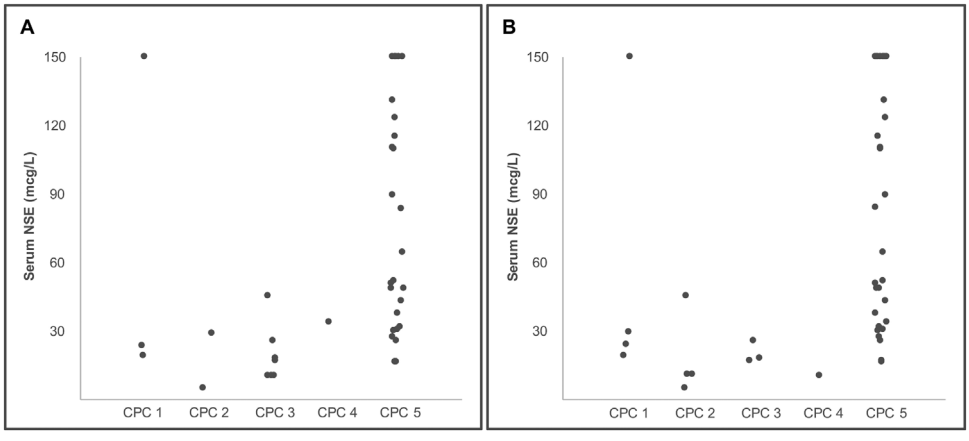

Fig. 2 – NSE level and CPC score.
NSE level and CPC score. The left panel (A) displays the distribution of NSE levels by discharge CPC score for all patients who had NSE measured between days 1–3 post-arrest, while the right panel (B) displays NSE levels by 6-month CPC score. The assay measured a minimum value of $<$5.0 mcg/L, which is plotted here as equal to 5.0 mcg/L, and a maximum value of $>$150.0 mcg/L, plotted here as equal to 150.0 mcg/L.

Table 2 – Predictive value of the American Academy of Neurology (AAN) guideline.

	TP, N	FP, N	TN, N	FN, N	*p*	FPR, % (95% CI)	Sensitivity, % (95% CI)
Discharge	111	2	22	91	<0.001	8 (1–26)	55 (48–62)
6 months	108	5	28	85	<0.001	15 (7–31)	56 (49–63)

Abbreviations: TP = true positive; FP = false positive; TN = true negative; FN = false negative; FPR = false positive rate.
P values are calculated for contingency tables.

Reduction in grey–white matter ratio and/or sulcal effacement on head CT performed well as a predictor of poor discharge outcome with a 0% FPR (95% CI, 0–17%; p = 0.1349). Diffuse hypoxic-ischaemic injury on MRI between days 2–6 had a FPR of 12% both at discharge (95% CI, 1–47%; p = 0.0033) and at 6 months (95% CI, 2–34%; p < 0.0001).

Discussion

Current neuroprognostication strategies after cardiac arrest are imprecise, stemming from studies marred by the bias of the self-fulfilling prophecyunavoidable in this setting to date. While the AAN, ERC/ESICM, and AHA all propose discrete and nuancedly different guidelines for neuroprognostication, they place value in common tools used in a multimodal manner—namely, the clinical examination, neuroimaging, and electrophysiologic and biochemical findings. However, predictions of poor outcome may be inaccurate, with several false positives emerging from this study cohort. Given that WLST certainly occurred, the performance of the guidelines here may only represent the best-case scenario—if patients had been followed without WLST, the FPR may well have been higher. As recovery is ongoing during the initial days post-arrest, early neuroprognostication may precede clinical improvement and thus underestimate the likelihood of recovery.

The ERC/ESICM guideline provided the best specificity, which hinged upon applying its multimodal algorithm only to those with absent or extensor motor responses. Further, perhaps the application of this guideline in practice could have prevented survival with poor outcome in two individuals (CPC 3 and 4). In contrast, the AAN guideline performed poorly within this cohort, with FPR higher than those reported, particularly for elevated NSE levels and for unfavourable motor responses combined with absent pupillary or corneal reflexes. All false positives occurred in TTM-treated patients, supporting the assertion that TTM may delay recovery. When prognosticating based on post-rewarming findings rather than post-ROSC, no patients were predicted to have a poor outcome.

The high specificity of the ERC/ESICM guideline is accompanied by relatively low sensitivity. The sensitivity for a "very likely" poor outcome ranged from 22 to 25%, while the criteria for a "likely" poor outcome demonstrated 33% sensitivity (Table 3). This, as well as its applicability only to patients with an absent or extensor motor response, represents a limitation of the guideline. Remarkably, the guideline predicted an indeterminate outcome for over 40% of the cohort based solely on a motor score greater than 2, though 67 of these patients ultimately had a poor outcome. In comparison, the AAN guideline demonstrated 55–56% sensitivity (Table 1), but with unacceptably low specificity. While both guidelines aim primarily to maximize specificity, the overall low sensitivities signify a critical gap in the field.

Table 3 – Predictive value of the European Resuscitation Council/European Society of Intensive Care Medicine (ERC/ESICM) guideline.

Discharge outcome							
	TP, N	FP, N	TN, N	FN, N	*p*	FPR, % (95% CI)	Sensitivity, % (95% CI)
"Very likely" poor outcome, day 3	33	0	24	150	0.02	0 (0–14)	18 (13–24)
"Very likely" poor outcome, day 4	32	0	24	133	0.02	0 (0–14)	19 (14–26)
"Very likely" poor outcome, day 5	26	0	24	119	0.03	0 (0–14)	18 (13–25)
"Likely" poor outcome	48	0	24	135	0.0016	0 (0–14)	26 (20–33)
6 month outcome							
	TP, N	FP, N	TN, N	FN, N	*p*	FPR, % (95% CI)	Sensitivity, % (95% CI)
"Very likely" poor outcome, day 3	33	0	33	141	0.003	0 (0–10)	19 (14–25)
"Very likely" poor outcome, day 4	32	0	33	124	0.002	0 (0–10)	21 (15–28)
"Very likely" poor outcome, day 5	26	0	33	110	0.003	0 (0–10)	19 (13–27)
"Likely" poor outcome	48	0	33	126	<0.001	0 (0–10)	28 (21–35)

Abbreviations: TP = true positive; FP = false positive; TN = true negative; FN = false negative; FPR = false positive rate.
P values are calculated for contingency tables.
[a]Based on one or both of the following: 1) no pupillary and corneal reflexes, and/or 2) bilaterally absent N20 potentials on somatosensory evoked potentials (SSEP).
[b]Defined as two or more of the following, with earliest prognostication beginning at 72 h: 1) myoclonic status epilepticus ≤48 h after return of spontaneous circulation (ROSC), 2) high neuron specific enolase levels at 48–72 h after ROSC, 3) unreactive burst-suppression or status epilepticus on EEG, 4) diffuse hypoxic-ischaemic brain injury on brain CT (≤24 h after ROSC) or MRI (days 2–5).

Table 4 – Predictive value of the American Heart Association (AHA) recommendations.

Discharge outcome

	TP, N	FP, N	TN, N	FN, N	*p*	FPR, % (95% CI)	Sensitivity, % (95% CI)
Bilaterally absent pupillary light reflex, day 3	51	0	24	130	<0.001	0 (0–14)	28 (22–35)
Bilaterally absent pupillary light reflex, day 4	43	0	24	121	0.002	0 (0–14)	26 (20–33)
Myoclonic status epilepticus at ≤72 h	60	0	24	142	<0.001	0 (0–14)	30 (24–36)
Burst suppression	24	0	16	157	0.23	0 (0–19)	13 (9–19)
Unreactive EEG to stimuli	92	0	9	48	<0.001	0 (0–30)	66 (58–73)
Status epilepticus	12	0	24	190	0.62	0 (0–14)	6 (3–10)
Absent N20 s on days 1–3	10	0	0	5	>0.99	0 (0–100)	67 (42–85)
NSE >33.0 mcg/L	22	0	3	9	0.04	0 (0–56)	71 (53–84)
NSE >78.9 mcg/L	15	0	3	16	0.24	0 (0–56)	48 (32–65)
Reduced GWR on head CT at ≤24 h	22	0	19	139	0.13	0 (0–17)	14 (9–20)
Diffuse hypoxic-ischemic injury on brain MRI, days 2–6	60	1	7	28	0.003	12 (1–47)	68 (58–77)

6 month outcome

	TP, N	FP, N	TN, N	FN, N	*p*	FPR, % (95% CI)	Sensitivity, % (95% CI)
Bilaterally absent pupillary light reflex, day 3	49	2	31	124	0.007	6 (1–20)	28 (22–35)
Bilaterally absent pupillary light reflex, day 4	42	1	32	114	0.002	3 (0–15)	27 (21–34)
Myoclonic status epilepticus at ≤72 h	59	1	32	134	<0.001	3 (0–15)	31 (25–37)
Burst suppression	24	0	24	149	0.05	0 (0–14)	14 (10–20)
Unreactive EEG to stimuli	92	0	17	40	<0.001	0 (0–18)	70 (61–77)
Status epilepticus	12	0	33	181	0.22	0 (0–10)	6 (4–11)
Absent N20 s on days 1–3	10	0	0	5	>0.99	0 (0–100)	67 (42–85)
NSE >33.0 mcg/L	21	1	3	9	0.12	25 (1–70)	70 (52–83)
NSE >78.9 mcg/L	15	0	4	15	0.11	0 (0–49)	50 (33–67)
Reduced GWR on head CT at ≤24 h	22	0	26	132	0.05	0 (0–13)	14 (10–21)
Diffuse hypoxic-ischemic injury on brain MRI, days 2–6	59	2	15	20	<0.001	12 (2–34)	75 (64–83)

Abbreviations: TP = true positive; FP = false positive; TN = true negative; FN = false negative; FPR = false positive rate; NSE = neuron specific enolase; GWR = grey–white matter ratio.
P values are calculated for contingency tables.

According to the AHA recommendations, absent pupillary reflexes on days 3 and 4 strongly predict poor outcome, with reported FPR of 0% (95% CI, 0–8%) in non-TTM-treated patients and 1% (95% CI, 0–3%) in TTM-treated patients.[22] In this cohort, reported specificities were upheld at hospital discharge. However, at 6 months, FPR for days 3 and 4 increased to 6% and 3%, respectively, with non-negligible CI. MSE performed similarly at 6 months, and diffuse hypoxic-ischaemic injury on MRI provided even lower specificity. Sensitivities were markedly variable, with absent pupillary reflexes demonstrating less than 30% sensitivity for a poor outcome (Table 4). Though these parameters are evaluated independently in this study, the AHA cautions that many of its recommendations should be considered in combination; however, no methodology is provided.[22]

Absent pupillary reflexes are well-studied as a reliable predictor of poor outcome,[23–27] yet our cohort demonstrated several cases of absent reflexes in patients who achieved a good outcome. These must be interpreted cautiously, as no standardized technique such as pupillometry was used. Without objective pupillary scoring, interrater reliability is low, and reactivity may be undetected.[28–30]

Notably, within this cohort, poor outcome was driven primarily by CPC 5, which comprised 69% of the cohort at 6 months; however, our cohort did include a relatively high proportion of CPC 3-4. Amongst those with discharge CPC 5, 77% died in the setting of WLST (Table 1). It is still possible that the incidence of poor outcome is inflated by self-fulfilling prophecy, and consequently so too are the specificities of each prognosticator. FPR may be underestimated given the rate of WLST, particularly within the first 5 days (55 patients). Patients with WLST on day 1 were excluded from the study (47 patients; Fig. 1), further biasing results toward underestimation of early WLST.

Thirteen patients (16% of survivors to discharge) improved from a poor discharge outcome to a good 6-month outcome. Other studies suggest that functional recovery after cardiac arrest occurs throughout the first year.[31,32] In this cohort, false positives emerged more frequently at 6 months, reflecting significant post-discharge improvement. Further research on long-term outcomes at serial time points may better characterize the scope of neurologic recovery and would lend itself well to improving neuroprognostic accuracy.

Study limitations

Due to the nature of a single-centre retrospective study, the generalizability of these findings is limited. SSEP, EEG, MRI and NSE data were not available in all subjects. Further, burst-suppression, status epilepticus, and absent N20 potentials were rare within this cohort, rendering their utility difficult to evaluate. Data were collected retrospectively and thus were limited by the accuracy and comprehensiveness of documentation. Clinical examination technique was neither standardized nor assessed, which may have led to false positives. Neuroimaging and electrophysiologic findings were abstracted from the final reports for these tests. CPC scores, abstracted from EMR documentation, were inherently limited by availability.

Neuroprognostication practices and implementation of WLST may represent the bias of our centre. Certain tests, including NSE and SSEP, were not routinely collected prior to 2015 due to practice patterns or

unavailability at this institution. Further, the study period captured evolving post-cardiac arrest care practices following the publication of the TTM trial in 2013,[33] thus capturing target temperatures ranging from 32 to 36 °C and evolving neuroprognostication practices with the introduction of protocols of care. Our institutional guidelines, introduced in 2013 and revised in 2015 (Fig. S1), favoured a multimodal approach at no earlier than 72 h. However, WLST decisions were at the discretion of the treating team, and this time window was not strictly followed in practice as demonstrated by our data.

CPC scoring, though utilized in each guideline, is not without limitations.[34–36] Mild to moderate cognitive deficits may not manifest as functional disability and can therefore be underestimated. Conversely, functional impairment is not necessarily secondary to arrest. Furthermore, cardiac arrest patients often have numerous comorbidities and may have diminished pre-arrest functional status, the extent of which is not quantified in the guidelines nor this study. Measuring CPC change from the pre-arrest state may be more useful for assessing neuroprognostic utility.

Each guideline cautions against the confounding effect of residual sedation. To the best extent possible, data were abstracted from the earliest time point consistent with guideline recommendations, at which time the effect of sedation was presumed to be negligible.

Conclusions

No gold standard currently exists for neuroprognostication of post-cardiac arrest survivors. Comparing the AAN, ERC/ESICM, and AHA guidelines, the ERC/ESICM guideline provides the best specificity for predicting poor outcome, though at the expense of significantly lower sensitivity. Future prospective initiatives should seek to better characterize the value of available neuroprognostic modalities, both independently and in a multimodal fashion, with respect to both discharge and long-term outcomes.

Conflicts of interest

Ms. Sonya E. Zhou reports no disclosures.

Dr. Carolina B. Maciel reports no disclosures.

Ms. Cora H. Ormseth reports no disclosures.

Dr. Rachel Beekman reports no disclosures.

Dr. Emily J. Gilmore reports no disclosures.

Dr. David M. Greer serves as Editor-in-Chief of *Seminars in Neurology* and has received compensation for medico-legal consultation.

Authors' declarations

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.resuscitation.2019.03.035.

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