Prognostic Value of the Neurological Examination in Cardiac Arrest Patients After Therapeutic Hypothermia

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Abstract

Objectives: Current prognostication guidelines for cardiac arrest (CA) survivors predate the use of therapeutic hypothermia (TH). The prognostic value and ideal timing of the neurological examination remain unknown in the setting of TH. **Design:** Patients (N = 291) admitted between 2007 and 2015 to Columbia University intensive care units for TH following CA had neurological examinations performed on days 1, 3, 5, and 7 postarrest. Absent pupillary light response (PLR), absent corneal reflexes (CRs), and Glasgow coma scores motor (GCS-M) no better than extension were considered poor examinations. Poor outcome was recorded as cerebral performance category score ≥ 3 at discharge and 1 year. Predictive values of examination maneuvers were calculated for each time point. **Main Results:** Among the 137 survivors to day 7, sensitivities and negative predictive values were low at all time points. The PLR had false positive rates (FPRs) of 0% and positive predictive values (PPV) of 100% from day 3 onward. For the CR and GCS-M, the FPRs decreased from day 3 to 5 (9% vs 3%; 21% vs 9%), while PPVs increased (91% vs 96%; 90% vs 95%). Excluding patients who died due to withdrawal of life-sustaining therapy (WLST) did not significantly affect FPRs or PPVs, nor did assessing outcome at 1 year. **Conclusions:** A poor neurological examination remains a strong predictor of poor outcome, both at hospital discharge and at 1 year, independent of WLST. Following TH, the predictive value of the examination is insufficient at day 3 and should be delayed until at least day 5, with some additional benefit beyond day 5.

Keywords

hypoxia-ischemia, brain, neurocritical care, cardiac arrest

Introduction

Cardiac arrest (CA) is associated with greater than 80% mortality, for both in-hospital and out-of-hospital arrests.^{1,2} Improved critical care led to increased survival, but neurological recovery is highly variable.³ Many of these patients remain comatose or in a vegetative state, prompting discussions of withdrawal of life-sustaining therapy (WLST). Premature WLST denies patients the opportunity for neurological recovery, while inappropriately continuing care uses limited health-care resources and prolongs the suffering of patients and families. Thus, accurate and timely prognostication is critical in these patients.

The 2006 American Academy of Neurology (AAN) practice parameter provided useful guidelines for prognostication in comatose CA survivors⁴ but was based on studies from the pre-hypothermia era. Thus, it must be interpreted with abundant caution in the patients undergoing the therapeutic

hypothermia (TH) protocol, which often requires sedation and neuromuscular blockade. The initial guidelines included 3 examination findings: absent pupillary light response (PLR), absent corneal reflexes (CRs), and a Glasgow coma score motor component (GCS-M) no better than extension.⁵ Patients with any of these findings at 72 hours had unanimously poor neurological outcomes.⁴ These findings have since been refuted by several studies showing higher false-positive rates at 72 hours in the setting of TH.^{6,7} Insufficient data exist on

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Figure 1. Patient selection.

the utility of the examination beyond 72 hours. It is hypothesized that the examination becomes more predictive further removed from TH.

Methods

Patients

All patients 18 years and older admitted to Columbia University Medical Center intensive care units (ICUs) following in-hospital or out-of-hospital CA between August 2007 and March 2015 were identified by research coordinators using diagnostic codes. Patients who did not undergo TH or died in the emergency department were not included in the study. Patients with missing demographic or neurological examination data were also excluded. The process for final patient selection is outlined in Figure 1. Full approval was given by our institutional ethics committee under protocol #AAAL4106. A waiver of informed consent was granted.

Induced Hypothermia

Based on our hospital policy, in all patients a neurological examination was performed immediately following return of spontaneous circulation (ROSC). Our cooling team (which includes a neurointensivist) was activated for all patients who did not return to their neurologic baseline, to determine if cooling was appropriate.⁸ For patients without a contraindication, TH was initiated with a target temperature range of 32°C to 34°C. This was achieved immediately with ice packs and ice-cold infusions and maintained in the ICU for 24 hours using a surface cooling device (Arctic Sun Temperature Management System; Medivance, Louisville,

Colorado) or intravascular device (Thermogard XP Temperature Management System; Zoll, Chelmsford, Massachusetts). A small minority of patients ($n = 4$, 3%) were cooled to a target temperature of 36°C, given a relative contraindication to cooling such as coagulopathy. Shivering was assessed using the bedside shivering assessment scale and controlled with the Columbia antishivering protocol.^{9,10} After 24 hours, patients were rewarmed to a core temperature of 37°C at the rate of 0.1°C/h. Sedation was discontinued after rewarming, unless required for patient comfort.

Data Collection and Outcomes

Demographics and arrest-related factors were recorded following Utstein guidelines, which included the site of CA, presence of witnesses, bystander cardiopulmonary resuscitation, initial rhythm, use of defibrillation, and time from arrest to ROSC.¹¹ Patient location and presence or absence of neurological consultation were recorded. Cerebral performance category (CPC) scores were calculated for each patient on admission and upon hospital discharge. Follow-up phone calls were conducted by an independent research team to assess CPC scores at 1 year postarrest. A CPC score of 3 to 5 was considered a poor neurologic outcome.

Neurological Assessment

After rewarming for an average of 24 hours, patients were examined on postarrest day 3, 5, and 7. When documenting the neurologic examination, the following priority was given to examiners: neurocritical care attending, neurology consultant for other ICUs, medical critical care attending, resident physician, and finally critical care nurse flow sheets. The highest priority examination for each patient on each day was chosen. Neurological examination included testing of brain stem reflexes (pupillary, corneal) and motor response to painful stimulation. Examinations explicitly documented as performed on sedation were excluded.

We restricted our analysis to patients who survived to day 7 and had all 3 components of the neurological examination documented each day. The decision regarding WLST was ultimately up to the attending physician and primary medical team. Our hospital's CA policy recommends general prognostication measures, including daily neurologic examination using the full outline of unresponsiveness score, daily neuron-specific enolase levels, continuous electroencephalogram (cEEG), somatosensory evoked potentials (SSEPs), magnetic resonance imaging between postarrest day 3 and 6, and formal neurological consultation.^{8,12} At the time of the study, no specific algorithm existed to synthesize this data, and the adherence to the policy was variable. Thus, the final decision was ultimately made by the primary team based on review of the available data as well as families' and patients' prior wishes.

Statistical Analysis

Poor examination findings (bilaterally absent PLR, absent CR, and GCS-M no better than extension), and poor outcomes (CPC score 3-5) were considered “positive.” The sensitivity, specificity, false positive rate (FPR), positive predictive value (PPV), and negative predictive value (NPV) were calculated for outcomes both at discharge and at 1 year. Exact confidence intervals (CIs) were calculated based on binomial distributions. A subanalysis was performed, excluding patients whose cause of death was WLST. The PPVs were compared between the 2 groups (all survivors vs those without WLST) using 2-sample *z* tests both at discharge and at 1 year.¹³ Calculations were carried out using STATA software (version 13.1; StataCorp, College Station, Texas). A *P* value of less than .05 was considered statistically significant.

Results

A total of 390 patients were identified. The TH was not implemented in 99 of these patients. Of the remaining 291, 150 survived to day 7. After excluding 13 patients for missing data, 137 patients were ultimately analyzed.

Table 1 compares the baseline characteristics for the 137 patients analyzed as well as the 141 nonsurvivors treated with hypothermia. Survivors were significantly younger than nonsurvivors (mean age 60 vs 67; *P* = .001). Out-of-hospital CAs were more common among the group of nonsurvivors (78% vs 66%; *P* = .02). Initial rhythm also varied between the groups. Ventricular fibrillation was more common among survivors, while asystole was seen more frequently among nonsurvivors (*P* < .001). Survivors had shorter average time to ROSC (20 vs 29 minutes; *P* ≤ .001).

Among survivors to day 7 postarrest, 25% (*n* = 34) had a good neurological recovery (CPC score 1-2), while 31% (*n* = 43) survived to discharge with poor neurologic recovery (CPC score 3-4) and 44% (*n* = 60) died. Among the patients who ultimately died, the cause of death was WLST in 63% (*n* = 38). Of note, 58% (*n* = 22) of these patients were medically unstable at the time of WLST. Other causes of death included rearrest, with do not resuscitate status in 23% (*n* = 14), brain death in 10% (*n* = 6), and CA with unsuccessful resuscitation in 3% (*n* = 2).

Neurological Examination

Among our final cohort, 37% (*n* = 51) were treated in the neurological ICU, 55% (*n* = 76) were treated in a medical ICU with neurological consultation, and 7% (*n* = 10) were treated in a medical ICU without neurological consultation. With respect to the examiners, 20% of all examinations were performed by neurocritical care attendings, 28% by consulting neurologists, 26% by medical critical care attendings, 10% by resident physicians, and 15% by critical care nurses.

The sensitivities, specificities, FPRs, and NPVs and PPVs for the GCS-M, CR, and PLR are given in Table 2. The

sensitivity and NPV of the neurological examination following CA are low at all time points. While a poor examination is predictive of poor outcome, numerous patients who did not meet our criteria for a “poor” examination still had poor outcomes, leading to a high false-negative rate and therefore low sensitivity and NPV.

We found higher FPRs among our patients for both the GCS-M and CR than those reported in the 2006 AAN practice parameter. On day 3, we found FPRs of 0.21 (95% CI = 0.09-0.38) for the GCS-M and 0.09 (95% CI = 0.02-0.24) for the CR. All 3 FPRs fell below 0.10 by day 5, as shown in Figure 2, with the GCS-M reaching 0.09 (95% CI = 0.02-0.24) and the CR reaching 0.03 (95% CI = 0.00-0.15). The PLR remained a strong predictor of poor outcome, with FPRs of 0.00 (95% CI = 0.00-0.10) at days 3, 5, and 7.

The PPVs of all neurological examination maneuvers increased with time. All 3 examinations reached at least 95% PPV by day 5, as shown in Figure 2. The GCS-M examination had the lowest PPVs. Corneal reflex PPVs were slightly higher and PLR PPVs were the highest, reaching 100% by day 3.

Absence of WLST

Our subanalysis of patients who did not die of WLST included 99 patients. The FPRs did not change as these calculations only include patients with good outcomes. While the PPVs decreased at each time point, these changes were not statistically significant at any point, as shown in Table 3.

Long-Term Outcomes

Of the 137 patients analyzed, 60 died prior to hospital discharge. The remaining 77 were reassessed for CPC score at 1 year postarrest; 73 (95%) were reachable and 4 (5%) were lost to follow-up. Among the survivors to discharge, 31 (41%) had a good neurological recovery at 1 year (CPC score 1-2), while 15 (20%) survived to discharge with poor neurologic recovery (CPC score 3-4) and 27 (35%) died. We reassessed the PPV of each examination maneuver at each time point with CPC score at 1 year as the new end point (supplemental Table 1). The sensitivities, specificities, FPRs, PPVs, and NPVs were not significantly different than those based on CPC score at hospital discharge.

Discussion

In the pre-TH era, the neurological examination was a vital component of prognostication following CA, as emphasized by the 2006 AAN practice parameter.⁴ Studies have since questioned the validity of the examination following treatment with TH, specifically reporting a higher number of false positives at the traditional 72-hour mark.^{6,7,14} Greer et al assessed the neurological examination beyond 72 hours among 500 patients with comatose, but only 200 were patients with CA

Table 1. Baseline Characteristics.

Characteristics	Survivors to 7 Days, n = 137	Nonsurvivors, n = 141	P Value
Age, mean (standard deviation)	60 (16)	67 (18)	.001^a
Gender, male, n (%)	78 (57)	78 (55)	.81
Prearrest comorbidities			
Body mass index, mean	30	29.5	.48
Hypertension, n (%)	78 (57)	88 (62)	.39
Myocardial infarction, n (%)	29 (21)	24 (17)	.45
Congestive heart failure, n (%)	40 (29)	41 (29)	1.00
Insulin-dependent diabetes mellitus, n (%)	16 (12)	15 (11)	.85
Noninsulin-dependent diabetes mellitus, n (%)	27 (20)	37 (26)	.20
Cerebrovascular disease, n (%)	15 (11)	14 (10)	.85
Renal disease, n (%)	34 (25)	32 (23)	.78
Liver disease, n (%)	7 (5)	9 (6)	.80
Smoking status, n (%)			.57
Current smoker	31 (23)	22 (16)	
Past smoker	42 (31)	43 (30)	
Never smoker	55 (40)	52 (37)	
Prearrest CPC score, n (%)			.15
CPC score 1	93 (68)	79 (56)	
CPC score 2	24 (18)	33 (23)	
CPC score 3	20 (15)	28 (20)	
CPC score 4	0 (0)	1 (1)	
OOH cardiac arrest, n (%)	90 (66)	110 (78)	.02^a
Initial rhythm, n (%)			<.001^a
Ventricular fibrillation	43 (31)	19 (13)	
Pulseless electrical activity	60 (44)	65 (46)	
Asystole	28 (20)	52 (37)	
Bystander CPR for OOH cardiac arrests, n (%)			.75
CPR	29 (35)	30 (32)	
Time to ROSC, mean	20	29	<.001^a
CPC score at discharge, n (%)			
CPC score 1	15 (11)		
CPC score 2	19 (14)		
CPC score 3	25 (18)		
CPC score 4	18 (13)		
CPC score 5	60 (44)		
CPC score at 1 year, n (%)			
CPC score 1	21 (16)		
CPC score 2	10 (8)		
CPC score 3	10 (8)		
CPC score 4	5 (4)		
CPC score 5	87 (65)		

Abbreviations: CPC score, cerebral performance category score; CPR, cardiopulmonary resuscitation; OOH, out-of-hospital; ROSC, return of spontaneous circulation.

Boldface type indicates significance ($P < 0.05$).

^aChi-square and Fisher exact tests were used to calculate P values for all dichotomous variables. Student t test was used to calculate P values for continuous variables.

and only a small minority were treated with TH.¹⁵ Our study focused on patients treated with TH and only included those surviving to at least day 7 to allow comparison of serial examinations. Among our cohort, no patients with absent PLR at day 3 went on to have good neurological recovery, similar to the 2006 guidelines. However, we found higher FPRs at 72 hours for both the CR and GCS-M, contrary to the pre-hypothermia guidelines but consistent with numerous recent studies.^{7,14,15}

Recent studies have acknowledged the confounding effect of sedation associated with hypothermia protocols, particularly the impact of sedation on neurological examination.^{16,17} The CR and motor examination appear particularly susceptible to sedative medications and response varies between patients depending on inherent cytochrome P450 drug metabolism.^{18,19} Lower core temperature depresses this system, decreasing drug metabolism.^{20,21} Thus, the effect of sedation likely lingers for a longer, though unpredictable, period in

Table 2. Prognostic Value of Neurological Examination Maneuvers.^a

Examination Maneuver	Day 1	Day 3	Day 5	Day 7
Motor examination				
Sensitivity	0.69 (0.59-0.78)	0.61 (0.51-0.71)	0.55 (0.45-0.65)	0.53 (0.43-0.63)
Specificity	0.62 (0.44-0.78)	0.79 (0.62-0.91)	0.91 (0.76-0.98)	0.94 (0.80-0.99)
False-positive rate	0.38 (0.22-0.56)	0.21 (0.09-0.38)	0.09 (0.02-0.24)	0.06 (0.01-0.20)
Positive predictive value	0.85 (0.75-0.91)	0.90 (0.80-0.96)	0.95 (0.86-0.99)	0.96 (0.88-1.00)
Negative predictive value	0.40 (0.26-0.54)	0.40 (0.28-0.53)	0.40 (0.29-0.52)	0.40 (0.29-0.52)
Corneal reflex				
Sensitivity	0.50 (0.40-0.60)	0.31 (0.22-0.41)	0.26 (0.18-0.36)	0.25 (0.17-0.35)
Specificity	0.67 (0.49-0.83)	0.91 (0.74-0.98)	0.97 (0.85-1.00)	1.00 (0.90-1.00)
False-positive rate	0.32 (0.17-0.51)	0.09 (0.02-0.24)	0.03 (0.00-0.15)	0.00 (0.00-0.10)
Positive predictive value	0.83 (0.71-0.91)	0.91 (0.77-0.98)	0.96 (0.82-1.00)	1.00 (0.87-1.00)
Negative predictive value	0.31 (0.21-0.43)	0.30 (0.22-0.40)	0.30 (0.22-0.40)	0.31 (0.22-0.40)
Pupillary light response				
Sensitivity	0.26 (0.18-0.35)	0.20 (0.13-0.29)	0.19 (0.12-0.28)	0.23 (0.16-0.33)
Specificity	0.88 (0.73-0.97)	1.00 (0.90-1.00)	1.00 (0.90-1.00)	1.00 (0.90-1.00)
False-positive rate	0.12 (0.03-0.27)	0.00 (0.00-0.10)	0.00 (0.00-0.10)	0.00 (0.00-0.10)
Positive predictive value	0.87 (0.70-0.96)	1.00 (0.84-1.00)	1.00 (0.83-1.00)	1.00 (0.86-1.00)
Negative predictive value	0.28 (0.20-0.38)	0.29 (0.21-0.38)	0.29 (0.21-0.38)	0.30 (0.21-0.39)

^aValues are 95% exact confidence interval. **Figure 2.** Prognostic value of neurological examination maneuvers.

patients treated with TH. The 2014 European Resuscitation Council and the European Society of Intensive Care Medicine guidelines recommend delaying prognostication beyond 72 hours only when interference from residual sedation or paralysis is suspected but do not address how to quantify this interference.¹⁶ We believe that the magnitude of interference cannot be adequately addressed in the clinical setting and thus prognostication should be uniformly delayed to ensure the effect of these medications has been eliminated.

Table 3. Positive Predictive Value of Neurological Examination Maneuvers in the Absence of Withdrawal of Life-Sustaining Therapy.^a

Examination Maneuver	All Survivors	Absence of WLST	P Value
Motor examination			
Day 1	0.85 (0.75-0.91)	0.78 (0.65-0.87)	.28
Day 3	0.90 (0.80-0.96)	0.84 (0.69-0.93)	.35
Day 5	0.95 (0.86-0.99)	0.91 (0.77-0.98)	.44
Day 7	0.97 (0.88-1.00)	0.94 (0.79-0.99)	.67
Corneal reflex			
Day 1	0.83 (0.71-0.91)	0.74 (0.56-0.86)	.26
Day 3	0.91 (0.77-0.98)	0.87 (0.66-0.98)	.63
Day 5	0.96 (0.82-1.00)	0.94 (0.71-1.00)	.77
Day 7	1.00 (0.87-1.00)	1.00 (0.78-1.00)	—
Pupillary light response			
Day 1	0.87 (0.70-0.96)	0.81 (0.58-0.95)	.56
Day 3	1.00 (0.84-1.00)	1.00 (0.77-1.00)	—
Day 5	1.00 (0.83-1.00)	1.00 (0.74-1.00)	—
Day 7	1.00 (0.86-1.00)	1.00 (0.77-1.00)	—

^aGroups were compared using 2-sample z tests for proportions.

In our study, when looking at serial neurological examinations, we found that specificity improves with time, thus we propose delaying the entire prognostication algorithm. While the PLR was 100% specific by day 3, the CR and GCS-M has significantly lower specificities at this time. The CR and GCS-M improved by day 5, with predictive values that were no longer significantly different from the PLR. The predictive value improved slightly between day 5 and day 7 but to a much lesser extent. We feel that all 3 examination components should be used during prognostication as each maneuver is susceptible to a number of confounders. In certain patients, the

PLR may be absent due to prior ocular surgery, ocular trauma, and sympathomimetic and parasympatholytic medications, while the CR may be decreased or even absent in chronic contact lens wearers.^{22,23} Utilizing more clinical measures decreases the risk of false positives and leads to a more robust prognostic workup.

In addition to looking at the examination over time, there are several other unique components to this study. First, we report the PPV of the neurological examination findings in addition to the traditionally studied FPRs. One study reported the PPV of examination components on a negative SSEP,²⁴ but to the best of our knowledge, no studies have reported the PPV of the neurological examination on prognosis. Instead they focus on specificity and FPR. While the FPR is a useful metric, especially in the research setting, it has little clinical significance for an individual patient and family. The PPV is useful in this context as it gives the percentage of patients who go on to have a poor outcome, given a poor examination finding at that point in the time. We feel that this allows clinicians to provide families with tangible expectations based on a patient's current clinical status. In our study, PPVs uniformly increased with time, with all 3 maneuvers reaching 95% by day 5.

Another unique aspect is our subanalysis, where we excluded patients who died following WLST. Historically, papers on CA outcomes are limited by an inherent "self-fulfilling prophecy." This refers to the fact that the decision to withdraw care is often based on a poor neurological examination. Thus, a poor examination finding might appear associated with poor outcome, but these results are confounded by WLST. We sought to address this issue by doing a subanalysis of patients whose cause of death was not WLST. A large number of patients in this study died following WLST due to medical instability or comorbidities as opposed to poor neurological prognosis. We included these patients in the WLST group, which may have been overly conservative but allowed us to definitively exclude any bias because of WLST. To our knowledge, this is the only study that has attempted to address this bias. The FPRs are not affected in the subanalysis, as these calculations are based only on patients with good outcomes. Instead, we used the PPV to identify the influence of WLST between all survivors and those who did not die on WLST. It must be noted that the majority of WLST occurred in patients who did not survive to 7 days and thus were not included in this study. However, in our select patient population of survivors to day 7, PPVs were not statistically different between the 2 groups, indicating that WLST did not significantly confound our results.

Finally, we repeated our analysis using CPC score at 1 year as an outcome measure. Several studies have addressed long-term outcome in patients with CA^{25,26} but have not looked at clinical measures during hospitalization and their value in predicting long-term outcome. We feel that long-term outcome is a more meaningful measure than the CPC score at hospital discharge. It is important to address long-term

outcomes early on in patient's hospital course because it can guide decision-making on the part of the family and medical team. We studied the neurological examination on postarrest day 3, 5, and 7 and found no difference in prediction of outcome at discharge or 1 year, suggesting that the examination at day 5 is a good predictor of both immediate and long-term neurological recovery.

While we suggest delaying prognostication beyond 72 hours, we appreciate the strain that postarrest care puts on patients, families, and the health-care system. In our study, poor neurological examination findings were reported in 9 patients on day 3 who ultimately achieved good neurological recovery. This number dropped to 3 patients by day 5. Thus, delaying prognostication until day 5 would theoretically save 6 lives or 4% of patients. There were still 2 false positives on day 7, which implies that delaying prognostication for all patients from day 5 to day 7 would save 1 additional patient or 0.7%. The presence of any false positives in the motor examination is concerning, which is why we support a multimodal prognostication scheme, including all 3 examination maneuvers as well as ancillary tests including serum biomarkers, cEEG, and imaging. Providers must weigh the prolonged suffering of the remaining patients and families, and the additional strain on the health-care system when deciding whether to continue care, but we feel that our data supports delaying prognostication until at least day 5 for all patients treated with TH.

There are several notable limitations to our study. First, we only analyzed patients who survived to day 7, allowing us to compare serial examinations. This inherently limits the generalizability of our findings, as we found significant differences between our group of survivors and nonsurvivors. As discussed, most of the WLST occurred in the first 7 days, so while we found no significant confounding in our sample, we likely did not appreciate the full extent of influence of WLST in our sample. Another limitation of our study was the variability in who performed the neurological examinations, based on setting and primary team. While we excluded examinations that were explicitly documented as performed on sedation, the retrospective nature of this study prevented a standardized approach to holding sedation. For patients on continuous sedation, it is the general ICU protocol to perform daily sedation holidays. For patients in the neurological ICU and examined by neurology consulting teams, the department's standard practice is to hold sedation for daily rounds and examination, thus these examinations were done off sedation. However, other ICUs do not necessarily follow this same protocol and unless explicitly noted, there was insufficient documentation to confirm the exact sedative dosing (or length of sedation holding) for each examination performed by a nonneurologist. Another limitation is that for patients discharged prior to 2012, follow-up phone calls were made more than 1 year postarrest and patients or families were asked to assess the functional status retrospectively, which introduced recall bias. A protocolized, prospective study is needed to address these issues.

Finally, a limitation of the neurological examination as a prognostic marker is its low sensitivity. While it remains specific, a good neurological examination does not necessarily predict good outcome. Thus, neurological examination alone should not be the only prognostic measure, rather it should be interpreted along with other clinical variables such as EEG, SSEP, serum biomarkers, and neuroimaging findings. Further studies in a prospective manner are needed looking at the neurological examination along with other prognostic variables to develop optimal prognostication guidelines.

Conclusion

In conclusion, we found that a poor neurological examination remains a strong predictor of neurological recovery, both at hospital discharge and at 1 year postarrest, independent of WLST. In the setting of TH, however, the predictive value of the examination at 72 hours is insufficient and should be delayed until at least day 5, with some additional benefit beyond day 5.

Declaration of Conflicting Interests

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Supplemental Material

Supplementary material for this article is available online.

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