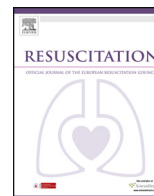




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### Clinical Paper

# Combining NSE and S100B with clinical examination findings to predict survival after resuscitation from cardiac arrest

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#### ABSTRACT

**Background:** Neuron specific enolase (NSE) and astroglial protein S100B are associated with outcome following resuscitation from cardiac arrest. We tested whether NSE and S100B levels are associated with illness severity on hospital arrival, and whether levels are independently associated with survival to hospital discharge after adjusting for initial illness severity.

**Methods:** Levels of NSE and S100B were obtained at arrival, 6, 12, 24, 48, and 72 h after successful resuscitation from cardiac arrest. Clinical data included demographics, Pittsburgh Cardiac Arrest Category (PCAC I–IV) and survival to hospital discharge. Univariable and multivariable predictive models including NSE and S-100B were created to predict survival. ROC analyses were performed to determine sensitivity and specificity of NSE and S-100B at each time interval.

**Results:** Of 77 comatose subjects, 5 did not receive therapeutic hypothermia and were excluded. Mean age was 59 (SD 16) years, with 58% male ( $N=42$ ), 72% out-of-hospital arrest ( $N=52$ ), and 43% VF/VT. Survival was 36% ( $N=26$ ). PCAC IV was associated with higher levels of NSE at 24 h ( $p=0.001$ ) and S100B at 24 h ( $p=0.005$ ). In the multivariate analysis, survival was associated with initial S100B level (OR 0.24; 95% CI 0.07–0.86). NSE values  $>49.5$  ng/mL at 48 h and NSE values  $>10.59$  ng/mL at 72 h predicted mortality. S100B levels  $>0.414$  ng/mL at 72 h predicted mortality.

**Conclusions:** More severe neurologic injury on initial examination is associated with higher levels of NSE and S100B. Elevated levels of S100B immediately following resuscitation were associated with death. Persistently elevated levels of NSE and S100B at 48 and 72 h were associated with death.

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## 1. Introduction

Many patients die from neurological injury after initial resuscitation from in-hospital and out-of-hospital cardiac arrest.<sup>1</sup> It is estimated that two-thirds of patients admitted to an intensive care unit after successful resuscitation from cardiac arrest do not survive to hospital discharge.<sup>2</sup> Physiological responses to prolonged systemic ischemia during cardiac arrest results in a post-cardiac arrest syndrome that includes brain injury, myocardial dysfunction, systemic inflammatory responses, as well as the precipitating disease.<sup>3</sup> Prolonged ischemic damage can result in severe anoxic-ischemic encephalopathy and coma. Failure to awaken is the most common

reason for withdrawal of care following successful resuscitation from cardiac arrest.<sup>4,5</sup>

Therapeutic hypothermia (TH) when used along with a neurocritical care bundle, has shown beneficial outcomes in comatose survivors of cardiac arrest.<sup>6,7</sup> The advent of TH has challenged prior standards for neurologic prognostication using the clinical examination, electroencephalogram, and serum markers such as neuron specific enolase (NSE) and S100B.<sup>8–10</sup> NSE is an intracellular enzyme located within neurons and neuroectodermal cells. Neuronal damage and interrupted integrity of the blood–brain barrier can result in NSE release into cerebral spinal fluid and blood. S100B protein is located in astrocytes and Schwann cells. Both of these proteins are elevated in blood after brain injury and stroke.<sup>10</sup> Several studies found that elevated NSE ( $28–33 \mu\text{g L}^{-1}$  at day 2) predicts poor outcome after cardiac arrest.<sup>11–13</sup> Other studies found that the cut-off NSE level for poor outcome in patients treated with TH is much higher ( $>78 \mu\text{g L}^{-1}$ ).<sup>14</sup> The predictive power of S100B after cardiac arrest is unclear. Proposed cut-off values have

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ranged from 0.05 to 0.18 ng/mL in patients treated with TH.<sup>15,16</sup> It is unclear what effect TH has on the usefulness of these biomarkers. A further limitation is that many studies used these serum biomarkers as criteria for withdrawal of care, thus creating a 'self-fulfilling prophecy.'

We speculated that an approach that integrates clinical data and laboratory measurements would better explain the observed variability in biomarker thresholds. The Post Cardiac Arrest Category (PCAC) is an illness severity score based on clinical variables during the first 6 h after return of spontaneous circulation (ROSC).<sup>5,17</sup> PCAC utilizes the Serial Organ Function Assessment (SOFA) subscales of cardiovascular and respiratory organ systems, as well as the Full Outline of Unresponsiveness (FOUR) subscale of motor and brainstem responses to categorize patients into four strata with distinct probabilities of survival and good outcome.<sup>5,17,18</sup> The purpose of this study is to determine how much serum NSE and S100B levels vary based on initial clinical examination, and to test whether the absolute values of or changes in these markers are associated with survival to hospital discharge after adjusting for PCAC category.

## 2. Methods

The University of Pittsburgh Institutional Review Board approved this prospective study. For the first 38 subjects, consent was obtained from the subject or their proxy. Blood samples were obtained at 0, 6, 12, 24, 48, and 72 h following resuscitation. Samples were stored at  $-80^{\circ}\text{C}$  until analysis. NSE and S100B were measured by ELISA according to manufacturer instructions (International Point of Care, Toronto, Ontario). However, due to low enrollment of subjects with more severe cardiopulmonary dysfunction, waiver of consent was granted for the remaining 48 patients. Subsequently, blood for these subjects was drawn at 0 and 24 h. Inclusion criteria were age greater than 18 years and cardiac arrest (defined as requiring chest compressions or rescue shock for a pulseless rhythm). Exclusion criteria were pregnancy, prisoner, withdrawal of care within 6 h of hospital arrival, preexisting do-not-resuscitate order, re-arrest with unsuccessful resuscitation within 6 h of hospital arrival, and arrest due to trauma. We also excluded subjects who were following commands after resuscitation, because they were believed to have minimal neurological injury and they were not eligible for TH.

### 2.1. Treatment protocol

In our facility, TH is typically induced with intravenous infusion of 20–30 cc/kg of  $4^{\circ}\text{C}$  saline solution, combined with surface cooling using cooling blankets and ice packs. Endovascular cooling is rarely used. The goal temperature was  $33^{\circ}\text{C}$ , however temperatures between  $32$  and  $34^{\circ}\text{C}$  were considered to be within the target range. Cooling duration was for 24 h after initiation of cooling. Temperature was monitored with esophageal temperature probes. Subjects were rewarmed at a goal rate of  $0.25^{\circ}\text{C/h}$ . Sedation with propofol or midazolam with fentanyl analgesia was recommended to prevent shivering. Paralysis was frequently employed during initiation of TH in our facility, but continuous infusions of paralytics once goal temperature has been achieved were rarely used.

Fluid infusion and use of vasopressors and inotropes were recommended to achieve a urine output of  $\geq 0.5\text{ mL/kg/h}$  and mean arterial pressure  $\geq 80\text{ mm Hg}$  to ensure adequate cerebral perfusion.<sup>19</sup> Vasopressor choices were based on individual clinician preference.

Clinical data included the initial SOFA cardiac and pulmonary subscores. These were summed into a single score (SOFA-CP). Similarly, the FOUR motor and brainstem subscores were summed into a single score (FOUR-MB). Based on these scores subjects 4

PCAC levels were determined: (I) awake; (II) moderate coma (not following commands but FOUR-MB  $> 4$ ) + mild cardiopulmonary dysfunction (SOFA-CP  $< 4$ ); (III) moderate coma (not following commands but FOUR-MB  $> 4$ ) + moderate-severe cardiopulmonary dysfunction (SOFA-CP  $\geq 4$ ); or (IV) deep coma (FOUR-MB  $\leq 4$ ) with any degree of cardiopulmonary dysfunction. These categories are calculated within the first 6 h of arrest. The primary outcome was survival to hospital discharge. Neurologic outcomes were assessed using cerebral performance category (CPC), modified Rankin Scale (mRS) and discharge disposition. A good outcome is defined as a CPC of 1–2, mRS of 0–3 or discharge to home or acute rehabilitation facility. All three outcomes are reported as they each measure different components of the subject's status.<sup>20</sup>

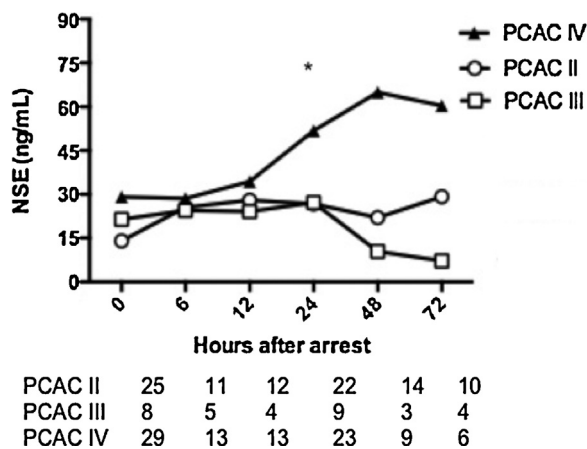
### 2.2. Neurologic prognostication

During the study, all subjects received an initial examination to determine the PCAC as outlined above. Examinations were completed daily thereafter by one of the post-cardiac arrest service physicians. All subjects received CT imaging of the brain to evaluate for early cerebral edema. Patients without a motor response to painful stimuli at 72 h received somatosensory evoked potentials. Magnetic resonance imaging was reserved for subjects who remained persistently comatose and demonstrated equivocal findings on other testing and examinations. During this study, continuous EEG monitoring was rarely employed.

Non-normal data were log-transformed. Levels of NSE and S100B at each time interval as well as the change in levels between arrival and 24 h were compared between PCAC strata using ANOVA. Single variable logistic regression was used to determine associations between clinical variables and survival. Multivariable logistic regression tested for independent associations between NSE and S100B levels and survival, after adjusting for PCAC and any other clinical variable with  $p < 0.1$  in the single variable regression. Hosmer–Lemeshow value was used to determine goodness of fit. Receiver operator curves (ROC) were created using 0, 24, 48 and 72-h serum levels as well as the change between 0 and 24 h levels. ROC curves were quantified using area under the curve (AUC). NSE and S100B values were analyzed by quartile for the ROC analyses. We calculated the 95% confidence intervals for the false positive rate (FPR) of any level of NSE or S100B that perfectly predicted in-hospital mortality. Because no PCAC III subjects were enrolled during the initial phase of the study requiring prospective consent, no ROC analysis was completed in PCAC III subjects for the 48 and 72-h times.

## 3. Results

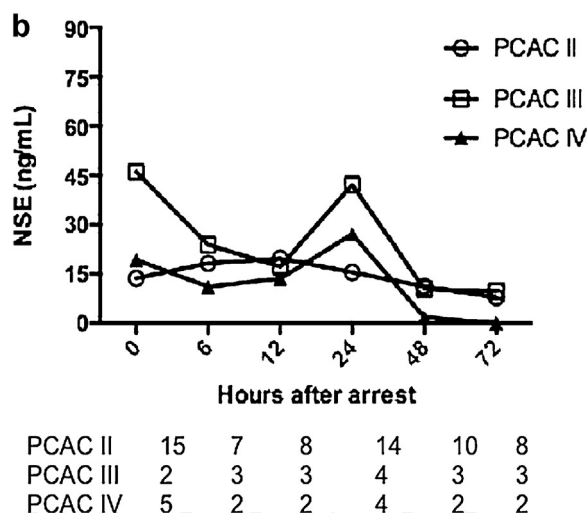
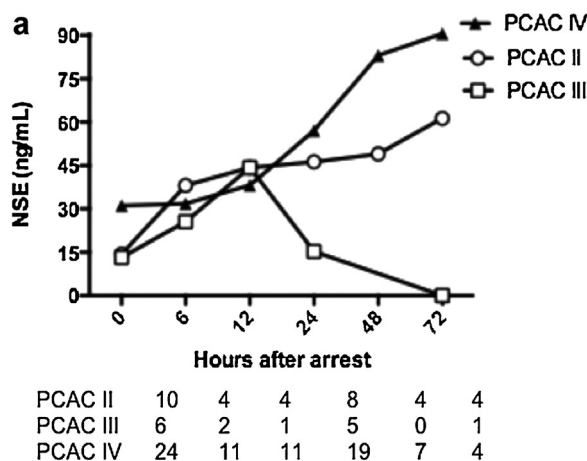
Of 86 subjects who provided blood samples, 9 were awake (PCAC-I) and were excluded from further analyses. An additional 5 subjects did not receive TH and were also excluded from analysis. Mean age was 59 (SD 16) years and most were male ( $n = 42$ , 58%). Out of hospital cardiac arrest made up 72% ( $n = 52$ ), with VF/VT the most common rhythm of arrest (43%). The distribution of clinical illness severity was PCAC II 39% ( $n = 28$ ), PCAC III 17% ( $n = 12$ ), and PCAC IV 44% ( $n = 32$ ). Survival was 36% ( $N = 26$ ). Median hospital length of stay was 8 days (IQR 4, 13) for the cohort. Survivors had a longer length of stay with a median of 12 days (IQR 9, 21) while non-survivors had a median stay of 4 days (IQR 3, 9;  $p < 0.001$ ). The most common etiology of death was poor neurologic prognosis (PCAC II  $N = 3$ , PCAC III  $N = 5$ , PCAC IV  $N = 13$ ) followed by multiple organ failure (PCAC II  $N = 3$ , PCAC III  $N = 2$ , PCAC IV  $N = 10$ ). A total of 8 subjects met brain death criteria (PCAC II  $N = 4$ , PCAC IV  $N = 4$ ), one could not be resuscitated from a second cardiac arrest (PCAC II



**Fig. 1.** Serum NSE stratified by PCAC. Values are means. Number of subjects at each time point is delineated below the time point (\*different from PCAC II and PCAC III,  $p < 0.05$ ).

and one had care withdrawn by family due to other chronic medical comorbidities (PCAC III).

A total of 3 subjects (4%) experienced good neurologic outcome by CPC, 4 subjects (6%) experienced good outcome by mRS and



**Fig. 2.** (A) Serum NSE level by PCAC in subjects who died. Values are means. Number of subjects at each time point is delineated below the time point. (B) Serum NSE level by PCAC in subjects who survived. Values are means. Number of subjects at each time point is delineated below the time point.

**Table 1**  
ROC analysis of NSE for predicting in-hospital mortality.

Neuron specific enolase	n	AUC	SE	95%CI
Hour 0				
PCAC II	25	0.53	0.11	0.31–0.75
PCAC III	8	0.34	0.17	0.00–0.69
PCAC IV	29	0.59	0.16	0.27–0.90
Hour 24				
PCAC II	22	0.75	0.09	0.57–0.94
PCAC III	9	0.53	0.18	0.18–0.89
PCAC IV	23	0.69	0.16	0.37–1.0
Change from hour 0–24				
PCAC II	22	0.74	0.1	0.55–0.93
PCAC III	8	0.38	0.16	0.06–0.69
PCAC IV	23	0.70	0.11	0.47–0.92
Hour 48				
PCAC II	14	0.85	0.12	0.62–1.0
PCAC IV	9	0.96	0.05	0.87–1.00
Hour 72				
PCAC II	10	0.65	0.14	0.37–0.93
PCAC IV	6	1.00	0.00	1.00–1.00

20 subjects (28%) experienced good outcome based on discharge disposition.

NSE levels were higher in PCAC IV subjects when compared to PCAC II and PCAC III subjects (Fig. 1). Post hoc comparison indicated that PCAC IV subjects had higher levels of NSE at 24 h ( $p = 0.005$ ). Rising NSE in each PCAC strata was associated with death, while decreasing NSE was associated with survival (Fig. 2). The results of the univariable analysis are reported in the Supplemental Table. Multivariable analysis reveals that the change in NSE between arrival and 24 h was not significant (OR = 0.97, CI: 0.93, 1.00) after adjusting for PCAC II (OR = 3.84, CI: 0.51, 28.83), PCAC IV (OR = 0.70, CI: 0.08, 5.76) and VF (OR = 2.62, CI: 0.62, 11.16) (Hosmer Lemeshow value = 0.75). No other NSE models demonstrated an association with survival.

Supplementary table related to this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.resuscitation.2014.04.020>.

### 3.1. ROC analysis for NSE

Neither NSE at 0 h, 24 h, or change in NSE from 0 to 24 h reliably predicted death. At 48 h, all PCAC II subjects with NSE values > 49.5 ng/mL (FPR = 0%; 95%CI: 0–80%) and all PCAC IV subjects with NSE values > 10.44 ng/mL (FPR = 0%; 95%CI: 0–54%) died. At 72 h, all PCAC IV subjects with NSE values > 10.59 ng/mL (FPR = 0%; 95%CI: 0–54%) died (Table 1).

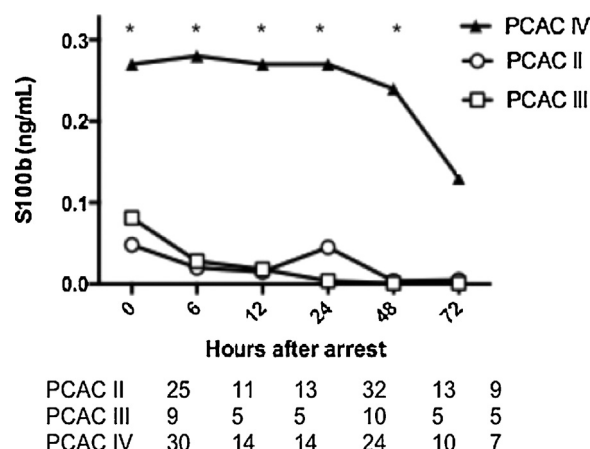
S100B, was higher in PCAC IV subjects when compared to PCAC II and III subjects at all time points except 72 h ( $p < 0.05$ ) (Fig. 3). Persistently elevated levels of S100B were associated with mortality, while decreasing levels were associated with survival (Fig. 4). In the multivariable analyses, elevated S100B levels at arrival were negatively associated with survival (OR 0.24; 95% CI 0.07–0.86), after adjusting for PCAC II (OR 7.10; 95% CI 0.55, 91.4), PCAC IV (OR 1.54; 95% CI 0.12, 20.3), and VF (OR 1.23; 95% CI 0.24, 6.24) (Hosmer Lemeshow value = 0.48).

### 3.2. ROC analysis for S100B

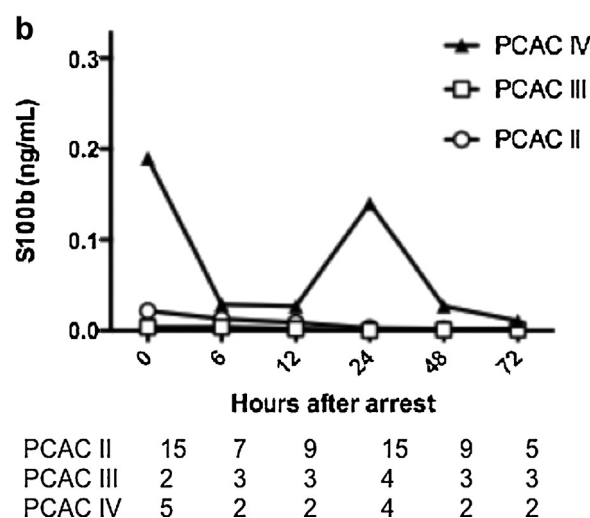
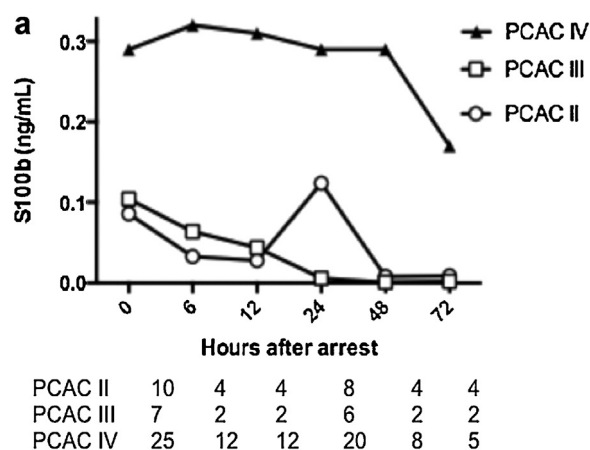
No S100B level at 0 h, 24 h, 48 h, nor any change from 0 to 24 h reliably predicted death. At 72 h, all PCAC IV subjects with S100B values > 0.414 ng/mL (FPR 0%; 95% CI 0–80%) died (Table 2).

## 4. Discussion

The results demonstrate that NSE and S100B levels are associated with depth of coma and illness severity. All subjects



**Fig. 3.** Serum S100B level stratified by PCAC. Values are means (\*different from PCAC II and PCAC III,  $p < 0.05$ ). Number of subjects at each time point is delineated below the time point.



**Fig. 4.** Serum S100B level by PCAC in subjects who died. Values are means. Number of subjects at each time point is delineated below the time point b Serum S100B level by PCAC in subjects who survived. Values are means. Number of subjects at each time point is delineated below the time point.

demonstrated elevated serum levels of NSE and S100B at the earliest time point. Levels normalize for the majority of subjects over a 72-h period. However, rising levels of NSE were seen in subjects who died. Rising NSE level may represent ongoing injury or

**Table 2**  
ROC analysis of S100B for predicting in-hospital mortality.

S100B	n	AUC	SE	95%CI
Hour 0				
Category II	25	0.56	0.10	0.36–0.76
III	9	0.50	0.20	0.11–0.89
IV	30	0.63	0.12	0.39–0.87
Hour 24				
PCAC II	32	0.67	0.11	0.45–0.88
PCAC III	10	0.73	0.13	0.48–0.99
PCAC IV	24	0.65	0.13	0.39–0.91
Change from hour 0–24				
PCAC II	25	0.57	0.10	0.37–0.77
PCAC III	9	0.41	0.14	0.13–0.69
PCAC IV	24	0.60	0.13	0.34–0.86
Hour 48				
PCAC II	13	0.75	0.13	0.50–0.99
PCAC IV	10	0.36	0.09	0.18–0.54
Hour 72				
PCAC II	9	0.46	0.16	0.14–0.78
PCAC IV	7	0.64	0.30	0.06–1.00

may result from the delayed appearance in blood of NSE released during the initial ischemia. Importantly, S100B levels were independently associated with survival in multivariable regression. This, along with the ROC analyses, demonstrates that combining S100B with the clinical examination may allow reliable determination of a cohort that will not awaken.

NSE levels in PCAC III subjects who died did not increase as in PCAC II and IV subjects. One potential reason may be that PCAC III subjects are more likely to die from multi-system organ failure as opposed to the neurologic devastation that accounts for mortality in PCAC II and IV subjects.<sup>5</sup> In addition, we were unable to enroll any PCAC III subjects in the portion of the study with all six time points.

While the initial level of S100B or NSE could not reliably predict survival, persistent elevation of NSE and S100B at 48 and 72 h may reflect irrecoverable injury. Levels of these proteins in blood might be useful confirmatory tests to predict outcome in patients after cardiac arrest.

## 5. Limitations

This study was performed in a single center, tertiary referral center with a small sample, resulting in wide confidence intervals for sensitivity and specificity. Additionally, the laboratory test necessary for serum NSE and S100B are not readily available in many hospitals in the United States. The fact that we measured NSE and S100B in the laboratory after all clinical care was completed is a strength of this study because the results were not used by treating teams to determined prognosis, avoiding the ‘self-fulfilling prophecy’ that affects many studies. While none of these subjects demonstrated clinical seizures, many patients have non-convulsive status epilepticus after cardiac arrest, which may also increase serum NSE, and S100B.<sup>21</sup> This study was completed prior to routine continuous EEG recordings in this population. Presence of seizures is an important confounder that should be considered in future studies.

## 6. Conclusions

NSE and S100B levels are associated with initial illness severity. A persistently elevated NSE level at 48 and 72 h is associated with death. An elevated S100B level at arrival or persistently elevated S100B level at 72 h is associated with death. Combining early clinical data and serum biomarkers may allow more rapid determination of survival in this population.



## Conflict of interest statement

The authors have no conflict of interest to report.

## Appendix A.

The Post Cardiac Arrest Service researchers are:

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## References

1. Nichol G, Thomas E, Callaway CW, et al. Regional variation in out-of-hospital cardiac arrest incidence and outcome. *J Am Med Assoc* 2008;300:1423–31.
2. Nolan JP, Soar J. Postresuscitation care: entering a new era. *Curr Opin Crit Care* 2010;16:216–22.
3. Neumar RW, Nolan JP, Adrie C, et al. Post-cardiac arrest syndrome: epidemiology, pathophysiology, treatment, and prognostication. A consensus statement from the International Liaison Committee on Resuscitation (American Heart Association, Australian and New Zealand Council on Resuscitation, European Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Asia, and the Resuscitation Council of Southern Africa); the American Heart Association Emergency Cardiovascular Care Committee; the Council on Cardiovascular Surgery and Anesthesia; the Council on Cardiopulmonary, Perioperative, and Critical Care; the Council on Clinical Cardiology; and the Stroke Council. *Circulation* 2008;118:2452–83.
4. Laver S, Farrow C, Turner D, Nolan J. Mode of death after admission to an intensive care unit following cardiac arrest. *Intensive Care Med* 2004;30:2126–8.
5. Rittenberger JC, Tisherman SA, Holm MB, Guyette FX, Callaway CW, et al. An early, novel illness severity score to predict outcome after cardiac arrest. *Resuscitation* 2011;82:1399–404.
6. Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *New Engl J Med* 2002;346:549–56.
7. Rittenberger JC, Guyette FX, Tisherman SA, DeVita MA, Alvarez RJ, Callaway CW. Outcomes of a hospital-wide plan to improve care of comatose 3 survivors of cardiac arrest. *Resuscitation* 2008;79:198–204.
8. Wijdicks EFM, Hijdra A, Young GB, Bassetti CL, Wiebe S. Quality Standards Subcommittee of the American Academy of Neurology. Practice parameter: prediction of outcome in comatose survivors after cardiopulmonary resuscitation (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2006;67:203–10.
9. Rittenberger JC, Sangl J, Wheeler M, Guyette FX, Callaway CW. Association between clinical examination and outcome after cardiac arrest. *Resuscitation* 2010;81:1128–32.
10. Cunningham R, Young IS, Winder J, et al. Serum neurone specific enolase (NSE) levels as an indicator of neuronal damage in patients with cerebral infarction. *Eur J Clin Invest* 1991;21:497–500.
11. Oksanen T, Tiainen M, Skrifvars MB, et al. Predictive power of serum NSE and OHCA score regarding 6-month neurologic outcome after out-of-hospital ventricular fibrillation and therapeutic hypothermia. *Resuscitation* 2009;80:165–70.
12. Rundgren M, Karlsson T, Nielsen N, Cronberg T, Johnsson P, Friberg H. Neuron specific enolase and S-100B as predictors of outcome after cardiac arrest and induced hypothermia. *Resuscitation* 2009;80:784–9.
13. Zandbergen E, Hijdra A, Koelman JH, et al. Prediction of poor outcome within the first 3 days of postanoxic coma. *Neurology* 2006;66:62–8.
14. Steffen I, Hasper D, Ploner CJ, et al. Mild therapeutic hypothermia alters neuron specific enolase as an outcome predictor after resuscitation: 97 prospective hypothermia patients compared to 133 historical non-hypothermia patients. *Crit Care (Lond, Engl)* 2010;14.
15. Böttiger B, Möbes S, Glätzer R, et al. Astroglial protein S-100 is an early and sensitive marker of hypoxic brain damage and outcome after cardiac arrest in humans. *Circulation* 2001;103:2694–8.
16. Mörtberg E, Zetterberg H, Nordmark J, Blennow K, Rosengren L, Rubertsson S. S-100B is superior to NSE, BDNF and GFAP in predicting outcome of resuscitation from cardiac arrest with hypothermia treatment. *Resuscitation* 2011;82:26–31.
17. Coppler P, Ahmed S, Sabedra A, et al. Validation of the Pittsburgh post-arrest illness severity score. *Crit Care Med* 2012;1–328 [Abstract 534].
18. Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med* 1996;22:707–10.
19. Sundgreen C, Larsen FS, Herzog TM, et al. Autoregulation of cerebral blood flow in patients resuscitated from cardiac arrest. *Stroke* 2001;32:128–32.
20. Rittenberger JC, Raina K, Kim YJ, Holm M, Callaway CW. Association between cerebral performance category, modified rankin scale, and discharge disposition after cardiac arrest. *Resuscitation* 2011;82:1036–40.
21. Rittenberger J, Popescu A, Brenner RP, Guyette FX, Callaway CW<ET AL>. Frequency and timing of nonconvulsive status epilepticus in comatose post-cardiac arrest subjects treated with hypothermia. *Neurocrit Care* 2012;16:114–22.