

## Research Article

# Predicting Survival with Good Neurological Outcome Within 24 Hours Following Out of Hospital Cardiac Arrest: The Application and Validation of a Novel Clinical Score

Aiham Albaeni<sup>1</sup>, Shaker M. Eid<sup>1\*</sup>, Dhananjay Vaidya<sup>2</sup> and Nisha Chandra-Strobos<sup>3</sup>

<sup>1</sup>Division of Hospital Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

<sup>2</sup>Division of General Internal Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

<sup>3</sup>Division of Cardiology, Johns Hopkins Bayview Medical Center, USA

Special Issue on

Cerebrovascular Disease

**Corresponding author**

Shaker M. Eid, Johns Hopkins School of Medicine, Research Director, Division of Hospital Medicine, Johns Hopkins Bayview Medical Center, 5200 Eastern Ave, MFL West 6th floor, Baltimore MD 21224, USA, Tel: 410-550-5018. Fax: 410-550-2972, E-mail: seid1@jhmi.edu

Submitted: 12 January 2014

Accepted: 20 January 2014

Published: 28 January 2014

**Copyright**

© 2014 Eid et al.

OPEN ACCESS

**Keywords**

- Cardiopulmonary resuscitation
- Heart arrest
- Sudden death
- Prognosis
- Survival

**Abstract**

**Background:** Despite 50 years of research, prognostication post cardiac arrest traditionally occurs at 72 hours. We tested the accuracy of a novel bedside score within 24 hours of hospital admission, in predicting neurologically intact survival.

**Methods:** We studied 192 adults following non-traumatic out-of-hospital cardiac arrest. In a 50% random modeling sample, a model for survival to discharge with good neurological outcome was developed using univariate analysis and stepwise multivariate logistic regression for predictor selection. The diagnostic efficiency of this modeled score was assessed in the remaining 50% sample using receiver operating characteristic (ROC) analysis.

**Results:** In this study, 20% of patients survived to discharge with good neurological outcome. The final logistic regression model in the modeling sample retained three predictors: initial rhythm Ventricular Fibrillation, Return of Spontaneous Circulation  $\leq$  20 minutes from collapse, and Brainstem Reflex Score  $\geq$  3 within 24 hours. These variables were used to develop a three-point Out of Hospital Cardiac Arrest score. The area under the (ROC) curve was 0.84 [95% CI, 0.75-0.93] in the modeling sample and 0.92 [95% CI, 0.87-0.98] in the validation sample. A score  $\geq$  2 predicted good neurological outcome with a sensitivity of 79%, a specificity of 92%, and a negative predictive value of 93%. A score  $\geq$  1 had a sensitivity of 100% and a negative predictive value of 100%; however, the specificity was only 55%.

**Conclusion:** This study demonstrates that a score based on clinical and easily accessible variables within 24 hours can predict neurologically intact survival following cardiac arrest.

**INTRODUCTION**

Despite standardized care guidelines for cardiac arrest patients that are uniform in many countries, outcomes are varied but remain generally poor [1,2]. Anoxic brain injury continues to be the major cause of death in this patient population. One of the most important tasks for health care providers is to correctly

identify those patients most likely to survive to hospital discharge so that precious medical resources can be appropriately allocated.

Efforts have been devoted in the last 50 years to improve survival following cardiopulmonary resuscitation (CPR) [2-4], with one of the most important interventions being therapeutic hypothermia [5,6]. Clinical trials have identified factors that are

associated with improved survival post arrest, and have put forward predictive tools for such patients [7]. However, many of these predictive tools were developed in the 80s and 90s, prior to the advent of therapies like hypothermia that emerged in 2002 and require heavy sedation and the use of paralytics [5]. No studies have commented on how such sedation affects CNS recovery. Clinicians continue to rely on predictive tools that were developed in the 80s, while the relevance and applicability of such data to care in 2014 is unclear. Although a 2012 study has reported on a complex predictive score of 11 items, for patients with in-hospital cardiac arrest [8], the relevance of this predictive index to the broad more common entity of out of hospital arrest is unclear, due to the obvious heterogeneity of the two populations (i. e. inpatient Vs. outpatient cardiac arrest).

We chose to develop and study a simple clinical tool that applies primarily to patients surviving out of hospital arrest, is not technology driven, and possesses the ease of clinical application in all hospitals regardless of resource availability. In addition, we sought a tool that would not only possess incremental accuracy in predicting survival but also survival with good neurological outcome.

## METHODS

### Study design and population

Following Institutional Review Board (IRB) approval, we retrospectively studied 210 patients with non-traumatic out-of-hospital cardiac arrest who survived to hospital admission at a teaching university hospital between 2004 and 2010. All patients were older than 18 years of age. Resuscitation was delivered by emergency medical service (EMS) personnel and the emergency department staff according to the American Heart Association (AHA) guidelines as temporally relevant [2,9]. Data were collected using Utstein guidelines [10,11]. Cardiac arrest was defined as the absence of a palpable central pulse, apnea, and unresponsiveness. Resuscitation was defined as the act of attempting to maintain or restore life by establishing or maintaining airway, breathing and circulation through CPR, defibrillation and other related emergency care techniques [10,11]. Return of spontaneous circulation (ROSC) was defined as a period of 30 seconds or more of restored spontaneous circulation [10,11]. Down time (time from collapse to CPR), time from CPR to return of spontaneous circulation (ROSC), and time from collapse to ROSC were collected from EMS and emergency staff documentations. In case of unwitnessed arrest, the time of first detection for cardiac arrest was used as a substitute for the time of collapse. Neurological outcome at discharge was assessed according to Glasgow-Pittsburgh Cerebral Performance Categories scale (CPC) : CPC 1 is conscious and normal; CPC 2 conscious with moderate cerebral disability; CPC 3 conscious with severe cerebral disability; CPC 4 coma or vegetative state; and CPC 5 death [11]. Patients with CPC 1 or 2 were considered to have a good neurologic outcome while those with CPC 3, 4 or 5 were considered to have a bad neurologic outcome.

### Regional EMS Service

The study hospital is located in Maryland, and serves a mixed urban community where EMS has a 2-tiered response with first

responders being AED equipped. The hospital serves a population of more than one million, of which 71% are Caucasian.

### Usual ICU Care

The decision to initiate therapeutic hypothermia was made by an intensive care unit attending based on institutional guidelines. All patients treated with hypothermia received a standardized protocol of sedation with Fentanyl/Midazolam, and paralytics (Vecuronium). All therapies were continued for 24 hours following which passive rewarming occurred. Paralytics were then stopped and the use of sedation was only for patient comfort per Joint Commission on Accreditation of Healthcare Organizations (JCAHO) guidelines [12]. For all other post arrest patients (i. e. those not receiving hypothermia), sedation was based on clinical needs and was primarily for patient comfort and was determined by the Richmond Agitation-Sedation Scale (RAAS) [13,14].

Routine ICU care included a four hourly neurological assessment of the patient that involves assessment of Glasgow Coma Scale (GCS), pupillary reflexes, corneal reflexes, gag/cough reflexes, oculocephalic reflexes and spontaneous breathing. Routine care also included stopping all sedation each morning to perform accurate neurologic assessments and spontaneous breathing trials (sedation holiday). Neurological assessments were usually performed by the nurses but also repeated separately by the resident physicians, the ICU attending physician and often the consulting neurologist. In case of discrepancy between observers, the report of the attending/neurologist was selected to reflect the status of the patient.

### Brainstem Reflex Score (BRS)

The brainstem reflex score (BRS) was clinically reported in 2006 and was derived from five brainstem reflexes (1-Pupillary reflex, 2-Corneal reflex, 3-Cough/Gag reflex, 4-Oculocephalic reflex (Doll's eye), 5-Spontaneous breathing). Each reflex was given equal impact and assigned one point giving BRS a range from 0 (worst) to 5 (best) [15].

### Timing of neurological score assessment

Sequential BRS scores were recorded for all patients during 24 hours and the highest score for each patient, while off sedation, was used in the study whether therapeutic hypothermia was applied or not. For patients undergoing hypothermia therapy, the optimal 24-hour BRS score was primarily the BRS score prior to initiation of paralytics and hypothermia.

### Study variables and model development

The goal was to develop a score that predicts survival with good neurologic outcome after out-of-hospital cardiac arrest, using variables accepted to be associated with improved survival. Many studies have confirmed that an initial rhythm of VT/VF, bystander CPR and duration to ROSC were associated with improved outcomes [16–21]. Hence these and other variables were tested in univariate analysis including: initial rhythm VT/VF [1, 16–18], return of spontaneous circulation (ROSC) less than or equal to 20 minutes from collapse [16,19], the presence of bystander CPR [16,20,21], Brainstem Reflex Score (BRS) within 24 hours post arrest more or equal to 3 [15,22], the use

of therapeutic hypothermia [5,6], down time less or equal to 5 minutes [23,24], age less than 75 years [25,26], the use of more than three doses of epinephrine during CPR [27], witnessed arrest [1], location of arrest [28], and gender [29].

### Patient group allocation

Of 210 eligible patients, 18 were excluded for missing data. The remaining 192 patients were randomly divided into two samples: a modeling sample of 96 patients and a validation sample of 96 patients.

### Data analysis

All variables used were categorical and continuous variables were dichotomized. We tabulated descriptive statistics for both the modeling and validation samples.

In the modeling sample, we worked to generate a predictive score. Univariate analyses were performed on all eleven variables of interest to explore association with survival to discharge with good neurological outcome (cerebral performance category of 1 or 2) using Chi square test. Variables that had a statistically significant association ( $p < 0.05$ ) with neurologically intact survival in univariate analyses were then included through a forward stepwise selection in a multivariable logistic regression model.

Beta-coefficients of multivariate logistic regression were used to inform the building of a simplified prediction score. Variables were given an equal weight of one score point if the 95% confidence intervals of the beta coefficients overlapped. The diagnostic efficiency of the score was assessed using the receiver operating characteristic curve (ROC) analysis in the validation sample [30]. Hosmer-Lemeshow goodness of fit test was used to assess the fitness of the developed model, and sensitivity analysis was performed to evaluate model performance with regards to ACLS guidelines changes, therapeutic hypothermia,

and care withdrawal. The sensitivity, specificity; positive and negative predictive values of the score at different thresholds were assessed in the validation sample.

## RESULTS

### Patient demographics

During the study period, 210 consecutive patients were admitted to the ICU with OHCA and 192 were analyzed after meeting inclusion criteria. The modeling and validation samples were comparable in terms of major comorbidities (Table 1). The mean age was 64 years ( $SD \pm 15$ ), 52% were male, 72% Caucasian, and 27% African American. Coronary artery disease was present in 41% of patients and congestive heart failure in 35%.

Cardiac arrest characteristics are shown in Table 2. The initial rhythm was Ventricular Fibrillation or Tachycardia in 42 patients (22%) ; 46 patients (24%) survived to hospital discharge, of those 38/46 (83%) survived to discharge with good neurological outcome; ROSC occurred within 20 minutes from collapse in 76 patients (39 %). Brainstem reflex score was  $\geq 3$  within 24 hours from admission in 44 patients (23%), and therapeutic hypothermia was used in 88 patients (46 %). Out of these 88 patients, 24 patients had VF/VT and 64 had PEA/Asystole as their initial arrest rhythm.

### Univariate and multivariate analyses

Eleven variables were tested in univariate analysis to generate the prediction equation. Five variables emerged as being predictive of survival with good neurologic outcome; 4 of which were associated with improved likelihood of neurologically intact survival, (initial rhythm of VF/VT, ROSC  $\leq 20$  minutes from arrest, BRS  $\geq 3$  within 24 hours of arrest, and down time  $\leq 5$  minutes) while the use of 3 or more doses of epinephrine during CPR worsened outcome (Table 3). The five variables were

**Table 1:** Patient Demographics for Development and Validation Samples.

Characteristics	All Patients N=192	Development Sample N=96	Validation Sample N=96	P Value
Mean age, years (SD)	64 (15)	66 (14)	62 (17)	0.07
Male sex, n (%)	108 (52)	60 (62.5)	48 (50)	0.08
Caucasians, n (%)	139 (72)	72 (75)	67 (70)	0.42
Tobacco use, n (%)	136 (71)	65 (68)	71 (74)	0.39
End stage renal disease, n (%)	16 (8.3)	8 (8.3)	8 (8.3)	1.00
CVA/TIA, n (%)	33 (17)	22 (23)	11 (11.4)	0.03
Diabetes Mellitus, n (%)	70 (36)	36 (37)	34 (35)	0.76
Hypertension, n (%)	138 (72)	70 (73)	68 (71)	0.74
Cancer, n (%)	34 (18)	21 (22)	13 (13.5)	0.13
Peripheral vascular disease, n (%)	24 (12.5)	16 (16.6)	8 (8.3)	0.08
Coronary artery disease, n (%)	78 (41)	42 (44)	36 (37)	0.37
Congestive heart failure, n (%)	68 (35)	33 (34)	35 (36)	0.76
Chronic obstructive pulmonary disease, n (%)	63 (33)	33 (34)	30 (31)	0.64
Hyperlipidemia, n (%)	84 (44)	49 (51)	35 (36)	0.04
Liver Disease, n (%)	13 (6.7)	5 (5.2)	8 (8.3)	0.38

CVA/TIA : Cerebrovascular Accident/ Transient Ischemic Attack

**Table 2:** Cardiac Arrest Characteristics in the Development and Validation Samples.

Characteristics	All Patients N=192	Development Sample N=96	Validation Sample N=96	P Value
Witnessed arrest, n (%)	139 (72)	65 (68)	74 (77)	0.14
Bystander CPR, n (%)	60 (31)	28 (29)	32 (33)	0.53
Initial Rhythm VF/VT, n (%)	42 (22)	20 (21)	22 (23)	0.72
ROSC ≤ 20 minutes, n (%)	76 (39)	41 (42)	35 (36)	0.37
Use of ≥3 doses of epinephrine, n (%)	106 (55)	51 (53)	55 (57)	0.56
Hypothermia therapy, n (%)	88 (46)	46 (48)	42 (44)	0.56
BRS at 24 hours ≥ 3, n (%)	44 (23)	19 (20)	25 (26)	0.30
Survival to Hospital discharge with good neurological outcome (CPC=1, 2), n (%)	38 (20)	19 (20)	19 (20)	1.00
Down time ≤ 5 minutes, n (%)	103 (54)	47 (49)	56 (58)	0.19
Arrest Location, n (%)				
Private	126 (66)	63 (66)	63 (66)	0.22
Public	16 (8.3)	11 (11.4)	5 (5.2)	
Other	50 (26)	22 (23)	28 (29)	

ROSC: return of spontaneous circulation, BRS: brain reflex score, CPR: cardiopulmonary resuscitation, VF/VT: ventricular fibrillation / ventricular tachycardia, CPC: cerebral performance category, Private Location: home, nursing home, Public Location: street or highway, public building, or other public property, Other Location: emergency department, ambulance, or clinic.

**Table 3:** Results of Univariate Analysis in the Development Sample.

Study Variables	N	Survivors with Good Neurological Outcome (CPC 1 or 2), n (%)	P Value
Witnessed arrest			0.08
Yes	65	16 (25)	
No	31	3 (10)	
Bystander CPR			0.76
Yes	28	5 (18)	
No	68	14 (21)	
Initial rhythm VF/VT			0.01
Yes	20	8 (40)	
No	76	11 (14)	
ROSC ≤ 20 minutes			<0.001
Yes	41	16 (39)	
No	55	3 (5)	
Use of ≥3 doses of epinephrine			0.009
Yes	51	5 (10)	
No	45	14 (31)	
Hypothermia therapy			0.33
Yes	46	11 (24)	
No	50	8 (16)	
BRS within 24 hours ≥ 3			0.001
Yes	19	9 (47)	
No	77	10 (13)	
Down time ≤ 5 minutes			0.01
Yes	47	14 (30)	
No	49	5 (10)	
Age ≥ 75 years			0.10
Yes	30	3 (10)	
No	66	16 (25)	

Gender			0.32
Male	60	10 (17)	
Female	36	9 (25)	
Arrest Location			0.08
Private	63	9 (14)	
Public	11	2 (18)	
Other	22	8 (36)	

ROSC: return of spontaneous circulation, BRS: brain reflex score, CPR: cardiopulmonary resuscitation, VF/VT: ventricular fibrillation / ventricular tachycardia, CPC: cerebral performance category, Private location: home, nursing home, Public location: street or highway, public building, or other public property, Other location: emergency department, ambulance, or clinic.

subsequently included through a forward stepwise selection in developing a multivariable logistic regression model.

Multivariate analysis identified three predictive variables (key variables) that retained statistically significant association with survival with good neurologic outcome ( $P < 0.05$ ) (initial rhythm VF/VT, ROSC ≤ 20 minutes, BRS ≥ 3 within 24 hours) (Table 4).

### Prediction score and validation

Regression coefficients of the 3 key variables were used to develop a score that would predict the probability of survival with good neurological outcome. Each variable was given an equal weight as previously mentioned to generate a prediction score from 0 to 3 with the presence or absence of any combinations of these 3 key variables (Table 5). Of the patients who had only one favorable predictor (OHCA score=1), only 12% survived with good neurological outcome. The presence of any two favorable predictors (OHCA score=2) increased the probability to 64%, and the presence of all three favorable predictors (OHCA score=3) in any patient further increased the probability to 86%.

The area under the curve for the modeling sample was 0.84 [95% confidence interval (0.75-0.93)]. In the validation sample the area under the curve was 0.92 [95% confidence interval

**Table 4:** Beta Coefficient and Odds Ratio of Multivariable Logistic Regression Model.

Variables	Beta Coefficient	95% Confidence Interval	Odds Ratio	95% Confidence Interval	P Value
Initial rhythm VF/VT	1.65	0.28-3.02	5.21	1.32-20.53	0.018
ROSC ≤ 20 minutes	2	0.61-3.40	7.45	1.84-30.18	0.005
BRS ≥ 3 within 24 hours	1.63	0.27-2.99	5.11	1.31-19.91	0.019

VF/VT: ventricular fibrillation / ventricular tachycardia, ROSC: return of spontaneous circulation, BRS: brainstem reflex score.

**Table 5:** OHCA Score at Different Thresholds (95% CI).

OHCA Score	Probability of Survival	Sensitivity	Specificity	PPV	NPV
0	0%	100%	0%	22% (10-34)	-
1	12%	100%	55% (48-62)	39% (28-50)	100%
2	64%	79% (66-92)	92% (88-96)	72% (65-79)	93% (89-97)
3	86%	32% (17-47)	99% (98-100)	83% (77-89)	83% (77-89)

OHCA: out-of-hospital cardiac arrest, PPV: positive predictive value, NPV: negative predictive value.

(0.87-0.98)]. The P value for goodness of fit was 0.26, suggesting that the developed model reflected the outcome experienced in the validation sample (Supplement Table 6). Sensitivity analysis showed that our model was not affected by heterogeneity of therapeutic hypothermia, care withdrawal, or changes in ACLS guidelines.

### OHCA score sensitivity and specificity

Survival probability (with good neurological outcome), sensitivity, specificity, positive predictive value (PPV), and negative predictive values (NPV) at different score points for the validation sample are shown in Table 5. An OHCA score ≥ 2 predicted survival with good neurological outcome with a sensitivity of 79% [95% CI, 66-92%], a specificity of 92% [95% CI, 88-96%], a positive predictive value of 72% [95% CI, 65-79%], and a negative predictive value of 93% [95% CI, 89-97%]. Alternatively, OHCA score ≥1 predicted good neurological outcome with a sensitivity of 100%, a specificity of 55% [95% CI, 48-62%], a positive predictive value of 39% [95% CI, 28-50%] and a 100% negative predictive value.

## DISCUSSION

This study shows that a clinically derived simple prediction tool comprised of 3 readily available variables (initial rhythm VF/VT, ROSC ≤20 minutes, and BRS ≥ 3 within 24 hours) can predict neurologically intact survival in out of hospital cardiac arrest patients.

For many acute or chronic disease entities where outcomes are varied, the field of medicine has developed and validated scoring systems to help identify patients more likely to have a good outcome or identify those at high risk for complications (e.g. atrial fibrillation, pancreatitis) [31,32]. In all such instances the purpose has been to better treat patients and also to better allocate precious health care resources. No score is absolute, but serves to guide clinical decision making.

The fundamental goal of resuscitation is to maintain vital organ perfusion with the quintessential goal being good neurological recovery. Despite great efforts and advances in optimizing the management of cardiac arrest victims, post cardiac

arrest brain injury is common and often the major contributor to death [33]. Our study demonstrates a survival to discharge of 24% following admission post arrest. Of those discharged alive, 83% had a good neurological outcome (CPC 1, 2). These survival rates are directionally similar to those reported by McNally et al. who reported that of those discharged post arrest 72 % had a good neurological outcome [1].

### Predictors of neurological outcome

Efforts at prognosticating neurological recovery in cardiac arrest patients can be traced to the 1960s when the EEG was first used to predict outcome and was found to be a poor marker of recovery [34]. Several investigators have commented and reported on the poor outcome of patients who have absent pupillary light reflexes [7,22,35,36]. However, no single sign predicted a favorable outcome. Motor reflexes have also been invoked for predicting neurological survival. Although the presence of myoclonus on day 1 has been shown to be a poor prognosticator of outcome, the false positive rate can be as high as 8.8% [36]. Thus, clinicians are reticent to use this finding alone to prognosticate outcome given the likelihood that if one is using this criterion alone, one may erroneously miss a survivor nearly 10% of the time [36]. This has been the major criticism of relying on motor reflexes for prognostication.

In 1985 Levy et al. developed a clinical prediction tool to identify patients most likely to recover following cardiac arrest. Although many other tools and algorithms have been evaluated, the Levy paper remains the clinical corner stone for guiding clinical decision making in such patients [7]. The Levy study examined neurological recovery on admission, day one, day three, one and two weeks after arrest. It relied on the presence or absence of brainstem reflexes to predict survival. The data from this study showed that only two out of 57 patients in whom eye-closed coma lasts for three days regained independent function. Another study by Bell and Hodgson in 1974 reported the rarity of full recovery after coma lasting three days [37]. Thus evaluating neurological status at day three emerged as the recommended time for recovery assessment. Levy reported that if pupillary light reflexes were absent, no patient survived while those with

preserved pupillary light reflexes and spontaneous movements on day one recovered.

Multiple studies have evaluated the role of somatosensory evoked potentials in predicting outcome after cardiac arrest, and found that bilateral absence of N20 component after median nerve stimulation, can reliably predict death due to its low false positive rates. However, the usefulness of the presence of N20 response appeared to be limited due to low sensitivity and low positive predictive value [36,38,39].

Years later and after the advent of therapeutic hypothermia, these observations were broadly revalidated; however, the issue of how hypothermia and its attendant sedation affect brainstem reflexes was poorly addressed. In 2011, Bouwes et al. restudied the reliability of the neurological exam, median nerve sensory-evoked potentials (SEP), and neuron-specific enolase (NSE) in predicting outcome post hypothermia therapy. The study demonstrated that the absence of pupillary light reflex, corneal reflex at 72 hours or the bilateral absence of cortical N20 responses of the median nerve could reliably predict poor outcome [40]. However; Zandbergen et al. questioned the usefulness of SSEP as a diagnostic or predictive tool since it appeared to be subject to noise interference and inter observer variability [41]. In addition, our score is based on easily accessible variables that do not depend on technology that requires significant training for interpretation and performance and might not be available in all institutions.

### Neurological assessment scores: limitations and shortfalls

Using the parameters discussed above in addition to key demographics, others have developed scores to predict survival after cardiac arrest. A prospective study by Geocadin et al. reported that survivors had a higher initial median Brainstem Reflex Score (BRS= 4) than those who died (BRS=2.5) [15]. The absence of light or corneal reflexes has also been associated with a poor prognosis [7,22].

A well-calibrated score by Adrie et al. that predicted survival with good neurological outcome was developed on prospectively collected data and was validated in multiple institutions. However, it was developed before the era of hypothermia and validated on populations after the introduction of hypothermia [42]. Another score by Okada et al. utilized five readily available variables on admission to predict survival with good neurological outcome. It was developed only on patients who were treated with hypothermia; thus, its usefulness in other post arrest patients is unknown [43]. Using the Get-with-the- Guidelines-Resuscitation registry data base, a large prospective registry of in-hospital cardiac arrest, Chan et al. developed a complex score of eleven variables to predict survival with good neurological outcome after in-hospital cardiac arrest. Although the score was detailed, well calibrated, and developed on a large sample, it would be clinically unwieldy to use due to its inherent complexity. Such a score would be difficult to remember or implement in a busy ICU [8].

As a result, there was a need for a simple clinical score that is validated in cardiac arrest patients with and without therapeutic hypothermia, is capable of predicting neurologically intact

survival with promising accuracy as early as the first 24 hours after cardiac arrest, and is easy to use and implement in a busy environment such as the intensive care unit.

### Effect of sedation

Obviously when a paralytic is used, motor responses cannot be followed. Sedation on the other hand, to levels that are commonly used for patient comfort, should not impact brain stem reflexes deleteriously. However, it has been shown that obesity, and hypothermia delay the clearance of commonly used sedatives [44,45]; hence, the duration of effect may change but the magnitude of the effect should not be affected if sedation is appropriately titrated to a RASS score of negative 1 or 2 [13,14]. Several sedatives and drugs used nowadays sequester in fat and may thereby contribute to delayed awakening calling into question the “three day rule” as suggested by Levy et al. Also, hypothermia has been shown to decrease the metabolism of Fentanyl and Midazolam, commonly used for sedation post arrest and thus likely to affect the timing of neurological awakening [44,45]. This becomes extremely relevant since such drugs are almost universally used in post arrest patients. Therefore, the applicability of the Levy observations to clinical practice in 2014 is unclear.

Since a component of our score is assessment of brainstem reflexes, our study circumvents the limitations imposed by therapeutic hypothermia and sedation by calculating the best BRS score during the “sedation holiday” in the first 24 hours and before initiation of paralytics and therapeutic hypothermia in patients receiving this intervention.

### Clinical relevance and implications

The goal of this study was to develop a score that was incremental, simple, easy to use in daily clinical practice, and able to accurately estimate survival with good neurological outcome (CPC 1,2) post arrest. The score consisted of three easily accessible variables (ROSC $\leq$ 20 minutes, BRS $\geq$ 3 within 24 hours of arrest, initial rhythm VF/VT) and was found to be incremental in its association with neurologically intact survival. If the score was  $\geq$ 2, the sensitivity and specificity were high enough to predict survival with good neurological outcome. Additionally a score  $<$ 2 had a high negative predictive value (93-100%) with an extremely low likelihood of survival. No patient scored zero and survived to hospital discharge with good outcome in the validation sample, and only one did in the development sample.

The incremental nature of our score suggests that if all 3 variables are present during the first 24 hours after arrest, continued intensive care, while factoring in other clinical variables, would be more likely to be rewarded with a good probability of neurologically intact survival.

### Study limitations

Several limitations of this study should be considered. First, this study reflects a single institution experience where the score was internally validated on a sample size that is robust for most resuscitation studies (210 patients with 46 survivors of whom 38 had good neurological outcomes). The original Levy study comprised 210 patients and the Adrie study 340 patients. Second, this score is not intended to recommend further treatment;

however, if validated in a large prospectively collected data it has the potential to be a useful tool in the hands of physicians to help guide aggressiveness of care and optimize the appropriate use of resources. Furthermore, prospective validation of such a score may help families in making decisions that are consistent with their values and goals of care. Third, withdrawal of care in patients with poor prognosis has the potential of introducing a bias to the outcome examined in this population; however, when the model was tested in patients who did not have withdrawal of care, all three variables forming the score continued to be significant predictors of neurologically intact survival. Also, when we further tested the difference between those variables' beta coefficient, the difference was not significant (P value = 0.94) indicating that even in this subpopulation, all three variables can still be given an equal weight in building the final simple score from 0 to 3. Thus such bias did not have a significant effect on the predictive accuracy of the score. Fourth, despite the importance of SSEPs in predicting survival, this technique was not used in this study as our score relies on readily available clinical variables that can be measured at any institution without the need for sophisticated technology. Finally, the impact of percutaneous coronary intervention (PCI) on survival after out-of-hospital cardiac arrest was recently established in multiple studies [46,47]; however, it did not become a popular therapeutic tool until 2012 which is a time period beyond the analysis of this study and hence was not factored into the analytical design.

## CONCLUSION

Physicians continue to struggle with correctly prognosticating survival post cardiac arrest. The field of resuscitation medicine continues to use 1985 data to guide such decisions despite many therapeutic advents that directly call into question the validity of these observations. Multiple scores in recent years were developed to address the issue of prognostication but all were complex scores that employed clinical, laboratory and procedural inputs. We have identified an easy to use incremental clinical score that has the potential to guide treatment and better triage resources. Further testing of this score in different databases is justified to establish validation in a larger cohort.

## REFERENCES

1. McNally B, Robb R, Mehta M, Vellano K, Valderrama AL, Yoon PW, et al. Out-of-hospital cardiac arrest surveillance --- Cardiac Arrest Registry to Enhance Survival (CARES), United States, October 1, 2005--December 31, 2010. *MMWR Surveill Summ.* 2011; 60: 1-19.
2. Field JM, Hazinski MF, Sayre MR, Chameides L, Schexnayder SM, Hemphill R, et al. Part 1: executive summary: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation.* 2010; 122: S640-656.
3. Hazinski MF, Nolan JP, Billi JE, Böttiger BW, Bossaert L, de Caen AR, et al. Part 1: Executive summary: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations. *Circulation.* 2010; 122: S250-275.
4. [http://www.heart.org/HEARTORG/CPRAndECC/WhatisCPR/CPRFactsandStats/History-of-CPR\\_UCM\\_307549\\_Article.jsp](http://www.heart.org/HEARTORG/CPRAndECC/WhatisCPR/CPRFactsandStats/History-of-CPR_UCM_307549_Article.jsp)
5. Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med.* 2002; 346: 549-556.
6. Bernard SA, Gray TW, Buist MD, Jones BM, Silvester W, Gutteridge G, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med.* 2002; 346: 557-563.
7. Levy DE, Caronna JJ, Singer BH, Lapinski RH, Frydman H, Plum F. Predicting outcome from hypoxic-ischemic coma. *JAMA.* 1985; 253: 1420-1426.
8. Chan PS, Spertus JA, Krumholz HM, Berg RA, Li Y, Sasson C, et al. A validated prediction tool for initial survivors of in-hospital cardiac arrest. *Arch Intern Med.* 2012; 172: 947-953.
9. ECC Committee, Subcommittees and Task Forces of the American Heart Association. 2005 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation.* 2005; 112: IV1-203.
10. Jacobs I, Nadkarni V, Bahr J, Berg RA, Billi JE, Bossaert L, et al. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update and simplification of the Utstein templates for resuscitation registries: a statement for healthcare professionals from a task force of the International Liaison Committee on Resuscitation (American Heart Association, European Resuscitation Council, Australian Resuscitation Council, New Zealand Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Councils of Southern Africa). *Circulation.* 2004; 110: 3385-3397.
11. Cummins RO, Chamberlain DA, Abramson NS, Allen M, Baskett PJ, Becker L, et al. Recommended guidelines for uniform reporting of data from out-of-hospital cardiac arrest: the Utstein Style. A statement for health professionals from a task force of the American Heart Association, the European Resuscitation Council, the Heart and Stroke Foundation of Canada, and the Australian Resuscitation Council. *Circulation* 1991; 84: 960-975.
12. Joint Commission on Accreditation of Healthcare Organizations, Revisions to Anesthesia Care Standards: Comprehensive Accreditation Manual for Hospitals Oakbrook Terrace, IL. Joint Commission on Accreditation of Healthcare Organizations Department of Publications, 2001.
13. Ely EW, Truman B, Shintani A, Thomason JW, Wheeler AP, Gordon S, et al. Monitoring sedation status over time in ICU patients: reliability and validity of the Richmond Agitation-Sedation Scale (RASS). *JAMA.* 2003; 289: 2983-2991.
14. Sessler CN, Gosnell MS, Grap MJ, Brophy GM, O'Neal PV, Keane KA, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. *Am J Respir Crit Care Med.* 2002; 166: 1338-1344.
15. Geocadin RG, Buitrago MM, Torbey MT, Chandra-Strobos N, Williams MA, Kaplan PW. Neurologic prognosis and withdrawal of life support after resuscitation from cardiac arrest. *Neurology.* 2006; 67: 105-108.
16. Sasson C, Rogers MA, Dahl J, Kellermann AL. Predictors of survival from out-of-hospital cardiac arrest: a systematic review and meta-analysis. *Circ Cardiovasc Qual Outcomes.* 2010; 3: 63-81.
17. Herlitz J, Bång A, Gunnarsson J, Engdahl J, Karlson BW, Lindqvist J, et al. Factors associated with survival to hospital discharge among patients hospitalised alive after out of hospital cardiac arrest: change in outcome over 20 years in the community of Göteborg, Sweden. *Heart.* 2003; 89: 25-30.
18. Bunch TJ, White RD, Gersh BJ, Shen WK, Hammill SC, Packer DL. Outcomes and in-hospital treatment of out-of-hospital cardiac arrest patients resuscitated from ventricular fibrillation by early defibrillation. *Mayo Clin Proc.* 2004; 79: 613-619.
19. Oddo M, Ribordy V, Feihl F, Rossetti AO, Schaller MD, Chioldero R, et

- al. Early predictors of outcome in comatose survivors of ventricular fibrillation and non-ventricular fibrillation cardiac arrest treated with hypothermia: a prospective study. *Crit Care Med.* 2008; 36: 2296-2301.
20. Aufderheide TP, Yannopoulos D, Lick CJ, Myers B, Romig LA, Stothert JC, et al. Implementing the 2005 American Heart Association Guidelines improves outcomes after out-of-hospital cardiac arrest. *Heart Rhythm.* 2010; 7: 1357-1362.
21. Wissenberg M, Lippert FK, Folke F, Weeke P, Hansen CM, Christensen EF, et al. Association of national initiatives to improve cardiac arrest management with rates of bystander intervention and patient survival after out-of-hospital cardiac arrest. *JAMA.* 2013; 310: 1377-1384.
22. Booth CM, Boone RH, Tomlinson G, Detsky AS. Is this patient dead, vegetative, or severely neurologically impaired? Assessing outcome for comatose survivors of cardiac arrest. *JAMA.* 2004; 291: 870-879.
23. Valenzuela TD, Roe DJ, Cretin S, Spaite DW, Larsen MP. Estimating effectiveness of cardiac arrest interventions: a logistic regression survival model. *Circulation.* 1997; 96: 3308-3313.
24. Safar P. Cerebral resuscitation after cardiac arrest: research initiatives and future directions. *Ann Emerg Med.* 1993; 22: 324-349.
25. Herlitz J, Eek M, Engdahl J, Holmberg M, Holmberg S. Factors at resuscitation and outcome among patients suffering from out of hospital cardiac arrest in relation to age. *Resuscitation.* 2003; 58: 309-317.
26. Longstreth WT Jr, Cobb LA, Fahrenbruch CE, Copass MK. Does age affect outcomes of out-of-hospital cardiopulmonary resuscitation? *JAMA.* 1990; 264: 2109-2110.
27. Hagihara A, Hasegawa M, Abe T, Nagata T, Wakata Y, Miyazaki S. Prehospital epinephrine use and survival among patients with out-of-hospital cardiac arrest. *JAMA.* 2012; 307: 1161-1168.
28. Weisfeldt ML, Everson-Stewart S, Sitlani C, Rea T, Aufderheide TP, Atkins DL, et al. Ventricular tachyarrhythmias after cardiac arrest in public versus at home. *N Engl J Med.* 2011; 364: 313-321.
29. Herlitz J, Engdahl J, Svensson L, Young M, Angquist KA, Holmberg S. Is female sex associated with increased survival after out-of-hospital cardiac arrest? *Resuscitation.* 2004; 60: 197-203.
30. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology.* 1982; 143: 29-36.
31. Gage BF, Waterman AD, Shannon W, Boehler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA.* 2001; 285: 2864-2870.
32. Ranson JH, Rifkind KM, Roses DF, Fink SD, Eng K, Spencer FC. Prognostic signs and the role of operative management in acute pancreatitis. *Surg Gynecol Obstet.* 1974; 139: 69-81.
33. 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: 2126-2128.
34. Hockaday JM, Potts F, Epstein E, Bonazzi A, Schwab RS. Electroencephalographic changes in acute cerebral anoxia from cardiac or respiratory arrest. *Electroencephalogr Clin Neurophysiol.* 1965; 18: 575-586.
35. Levy DE, Bates D, Caronna JJ, Cartlidge NE, Knill-Jones RP, Lapinski RH, et al. Prognosis in nontraumatic coma. *Ann Intern Med.* 1981; 94: 293-301.
36. Wijdicks EF, 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: 203-210.
37. Bell JA, Hodgson HJ. Coma after cardiac arrest. *Brain.* 1974; 97: 361-372.
38. Chen R, Bolton CF, Young B. Prediction of outcome in patients with anoxic coma: a clinical and electrophysiologic study. *Crit Care Med.* 1996; 24: 672-678.
39. Madl C, Kramer L, Yeganehfar W, Eisenhuber E, Kranz A, Ratheiser K, et al. Detection of nontraumatic comatose patients with no benefit of intensive care treatment by recording of sensory evoked potentials. *Arch Neurol.* 1996; 53: 512-516.
40. Bouwes A, Binnekade JM, Kuiper MA, Bosch FH, Zandstra DF, Toornvliet AC, et al. Prognosis of coma after therapeutic hypothermia: a prospective cohort study. *Ann Neurol.* 2012; 71: 206-212.
41. Zandbergen EG, Hijdra A, de Haan RJ, van Dijk JG, Ongerboer de Visser BW, Spaans F, et al. Interobserver variation in the interpretation of SSEPs in anoxic-ischaemic coma. *Clin Neurophysiol.* 2006; 117: 1529-1535.
42. Adrie C, Cariou A, Mourvillier B, Laurent I, Dabbane H, Hantala F, et al. Predicting survival with good neurological recovery at hospital admission after successful resuscitation of out-of-hospital cardiac arrest: the OHCA score. *Eur Heart J.* 2006; 27: 2840-2845.
43. Okada K, Ohde S, Otani N, Sera T, Mochizuki T, Aoki M, et al. Prediction protocol for neurological outcome for survivors of out-of-hospital cardiac arrest treated with targeted temperature management. *Resuscitation.* 2012; 83: 734-739.
44. Empey PE, Miller TM, Philbrick AH, Melick JA, Kochanek PM, Poloyac SM. Mild hypothermia decreases fentanyl and midazolam steady-state clearance in a rat model of cardiac arrest. *Crit Care Med.* 2012; 40: 1221-1228.
45. Zhou J, Empey PE, Bies RR, Kochanek PM, Poloyac SM. Cardiac arrest and therapeutic hypothermia decrease isoform-specific cytochrome P450 drug metabolism. *Drug Metab Dispos.* 2011; 39: 2209-2218.
46. Gräsner JT, Meybohm P, Caliebe A, Böttiger BW, Wnent J, Messelken M, et al. Postresuscitation care with mild therapeutic hypothermia and coronary intervention after out-of-hospital cardiopulmonary resuscitation: a prospective registry analysis. *Crit Care.* 2011; 15: R61.
47. Dumas F, White L, Stubbs BA, Cariou A, Rea TD. Long-term prognosis following resuscitation from out of hospital cardiac arrest: role of percutaneous coronary intervention and therapeutic hypothermia. *J Am Coll Cardiol.* 2012; 60: 21-27.

#### Cite this article

Albaeni A, Eid SM, Vaidya D, Chandra-Strobos N (2014) Predicting Survival with Good Neurological Outcome Within 24 Hours Following Out of Hospital Cardiac Arrest: The Application and Validation of a Novel Clinical Score. *J Neurol Transl Neurosci* 2(1): 1041.