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Multimodal Monitoring Including Early EEG Improves Stratification of Brain Injury Severity after Pediatric Cardiac Arrest

Alexis A. Topjian, MD, MSCE[1], **Bingqing Zhang, MPH**[1,2], **Rui Xiao, PhD**[3], **France W. Fung, MD, MSc**[4,5], **Robert A. Berg, MD**[1], **Kathryn Graham, MLAS**[1], **Nicholas S. Abend, MD MSCE**[4,5]

[1]Department of Anesthesia and Critical Care Medicine, Children's Hospital of Philadelphia and University of Pennsylvania Perelman School of Medicine

[2]Data Science and Biostatistics Unit, Department of Biomedical and Health Informatics, Children's Hospital of Philadelphia

[3]Department of Biostatistics, Epidemiology, and Informatics, Perelman School of Medicine at the University of Pennsylvania

[4]Division of Neurology, Children's Hospital of Philadelphia

[5]Departments of Neurology and Pediatrics, University of Pennsylvania Perelman School of M Medicine

Abstract

Aims: Assessment of brain injury severity early after cardiac arrest (CA) may guide therapeutic interventions and help clinicians counsel families regarding neurologic prognosis. We aimed to determine whether adding EEG features to predictive models including clinical variables and examination signs increased the accuracy of short-term neurobehavioral outcome prediction.

Methods: This was a prospective, observational, single-center study of consecutive infants and children resuscitated from CA. Standardized EEG scoring was performed by an electroencephalographer for the initial EEG timepoint after return of spontaneous circulation (ROSC) and each 12-hour segment from the time of ROSC up to 48 hours. EEG Background Category was scored as: (1) normal; (2) slow-disorganized; (3) discontinuous or burst-suppression; or (4) attenuated-featureless. The primary outcome was neurobehavioral outcome at discharge from the Pediatric Intensive Care Unit. To develop the final predictive model, we compared areas under the receiver operating characteristic curves (AUROC) from models with varying combinations of Demographic/Arrest Variables, Examination Signs, and EEG Features.

Corresponding Author: Alexis Topjian, MD, MSCE Division of Pediatric Critical Care Children's Hospital of Philadelphia 34th Street and Civic Center Boulevard Philadelphia, PA 19104 topjian@email.chop.edu.

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Conflicts of interest

The authors have no conflicts of interest.

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Results: We evaluated 89 infants and children. Initial EEG Background Category was normal in 9 subjects (10%), slow-disorganized in 44 (49%), discontinuous or burst suppression in 22 (25%), and attenuated-featureless in 14 (16%). The final model included Demographic/Arrest Variables (witnessed status, doses of epinephrine, initial lactate after ROSC) and EEG Background Category which achieved AUROC of 0.9 for unfavorable neurobehavioral outcome and 0.83 for mortality.

Conclusions: The addition of standardized EEG Background Categories to readily available CA variables significantly improved early stratification of brain injury severity after pediatric CA.

Keywords

EEG; Cardiac Arrest; Pediatric; Outcome; Seizure

Introduction

Cardiac arrest (CA) occurs in more than 21,000 children each year in the United States,[1–3] survival rates range from 10-44%, and many survivors have substantial neurobehavioral disabilities.[4–7] Assessment of brain injury severity early after CA may guide therapeutic interventions and neuroprognostication. However, CA variables do not reliably predict outcomes and the examination may be confounded by interventions.[8–11] Therefore, neuroprognostication approaches vary across institutions,[12] and inter-rater reliability is only moderate.[13] This is concerning since withdrawal of life-sustaining technology due to expected unfavorable outcome is a common mode of death among children after CA.[14–16] Single modality approaches to stratify outcomes are imperfect and limited.[17–20] Objective multimodality approaches are needed to assess brain injury severity early after CA to target therapeutic interventions and guide neuroprognostication.

Continuous electroencephalographic monitoring (cEEG) is recommended after CA to identify non-convulsive seizures,[8, 21–23] and the American Heart Association has noted that “EEG in conjunction with other factors may be useful within the first 7 days.”[8] Prior studies demonstrate that specific EEG features are associated with outcome after pediatric CA,[24–32] but most utilized retrospective review of reports without standardized EEG terminology or assessment times. Further, some patients experience improvement or worsening of EEG background features over time,[33] and the clinical significance of these changes is uncertain.

We aimed to determine whether a multi-modal model that combined EEG features with clinical variables and examination signs was more predictive of neurobehavioral outcome and mortality than clinical variables alone. Additionally, we aimed to determine whether improvement or worsening in the EEG background over time was associated with outcome.

Materials and Methods

This was a single-center, prospective, observational study of consecutive infants and children resuscitated after CA and treated in the Pediatric Intensive Care Unit (PICU) at the Children’s Hospital of Philadelphia between September 2013 and February 2016. The study was approved by the Institutional Review Board. Informed consent was obtained from

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guardians of patients for data collection. EEG data from this cohort have been reported previously.[28, 33–35]

Data were collected using the Research Electronic Data Capture (REDCap)[36] and consisted of prospectively defined demographic, CA, post-CA care, examination, EEG, and outcome variables. Demographic, CA, and post- CA variables were abstracted from the medical record. The lowest pH and highest lactate in the first 24 hours after ROSC were evaluated.

Clinically-indicated cEEG was performed in all patients with encephalopathy following resuscitation from CA to screen for electroencephalographic seizures (ES) based on an institutional pathway aligned with guidelines and consensus statements.[21–23] Encephalopathy post-CA was defined as any patient not at baseline mental status with or without administration of sedatives. CEEG was initiated urgently (24/7 coverage) using portable Grass-Telefactor video-equipment with electrodes positioned according to the international 10-20 system using standard technical specifications.[22] EEG was interpreted by the Electroencephalography Service, and clinical management was provided by the Critical Care Medicine and Neurology Consultation Services. Standard post-CA management did not include the administration of prophylactic anti-seizure medications. However, both convulsive and non-convulsive seizures were generally treated.. Benzodiazepine infusions were often administered for sedation.

Full cEEG tracings were saved for research.. Standardized EEG scoring was performed by an electroencephalographer at cEEG initiation and 12-hour segments from the time of ROSC up to 48 hours post-ROSC, such that timing categories were 0-12, 12-24, 24-36, 36-48 hours post-ROSC.) We previously published EEG variable definitions for this dataset,[28] and the EEG categorization system was utilized in prior critical care EEG studies.[24, 37–43]

The primary outcome was the Pediatric Cerebral Performance Category (PCPC) score assessed at PICU discharge. PCPC is a validated six-point scale that categorizes functional impairment.[44] The pre-admission PCPC score was estimated based on information provided by parents/guardians or prior medical visits included in the electronic medical record. Unfavorable outcome was defined as a change in PCPC ≥1 that resulted in a hospital discharge PCPC score of 3-6.[45, 46] The secondary outcome was mortality.

Statistical analyses were performed using SAS software version 9.4 (SAS Institute Inc, Cary, NC). We report summary statistics as medians and interquartile ranges (IQR) for continuous variables and counts and proportions for categorical variables. We explored the difference in patients' demographic, CA, post-CA care, examination signs, and outcome variables among EEG Background Category groups assessed at cEEG initiation using ANOVA or Kruskal Wallis test for continuous variables and counts and Chi-square test or Fisher's exact test for categorical variables, as appropriate. We performed the same analyses for unfavorable neurobehavioral outcome and mortality except that two-sample t-test or Wilcoxon Rank Sum test were used for continuous variables and counts. Variables associated with outcomes in univariate analysis (p-value <0.2) were included in subsequent multivariable logistic regression models (statistically derived models). Former premature status and trauma as the

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cause of CA were not included in the model because all these patients had unfavorable neurobehavioral outcomes.

To develop a clinically derived multi-modal prediction model, we considered Demographics/Arrest Variables (CA location, witnessed status, epinephrine doses, lactate post-ROSC), Examination Signs at 24-hours following ROSC (gag, cough, and pupillary reactivity) and EEG Features (initial Background EEG Category and stage 2 sleep architecture). We compared areas under the receiver operating characteristic (AUROC) curves between different models using Delong's test for two correlated ROC curves.[47] The complete case analysis was applied for the models with missing at random assumption.

To address the impact of changes in EEG Background Category over time, we calculated the difference between EEG Background Category assessed at cEEG initiation and during successive 12-hour epochs. Positive or negative numbers indicated worsening or improvement in EEG Background Category, respectively. A change in one, two, or three categories was one, two, or three points, respectively. We performed sub-analyses on: (1) patients with non-attenuated-featureless initial EEG Background Category to classify EEG changes into worsened versus not worsened, and (2) patients with non-normal initial EEG Background Category to classify EEG changes into improved versus not improved. We analyzed the association between outcome with worsening or improving EEG Background Category using Fisher's exact test for each subgroup.

Results

We evaluated 89 subjects. Supplemental Table 1 provides subject characteristics. The median age was 2.1 (IQR 0.27, 9.1) years. Fifty-six (63%) subjects were male. CA occurred in-hospital in 58 subjects (65%), and 64 (72%) were witnessed. The most common initial rhythms were bradycardia in 33 subjects (37%), asystole in 16 subjects (18%), and pulseless electrical activity in 10 subjects (11%). The median lactate after ROSC was 5.0 mmol/L (IQR 2.8, 8.4), and the mean lowest pH was 7.16 (+/− 0.19).

All cEEG recordings were initiated before or on the same day as CA. The median duration from ROSC to cEEG initiation was 6.9 hours (IQR 4.4, 11.5). The median duration of cEEG was 48 hours (IQR 34, 72). The EEG Background Category at cEEG initiation was normal in 9 subjects (10%), slow-disorganized in 44 subjects (49%), discontinuous or burst-suppression in 22 subjects (25%) and attenuated-featureless in 14 subjects (16%). Twenty-three subjects (26%) had stage 2 sleep architecture, and 41 subjects (46%) had EEG variability/reactivity. Seven subjects (8%) had ES, including six subjects with electroencephalographic status epilepticus.

Initial EEG Background Category was associated with age, weight, shock as cause of CA, and the administration of vasoactive infusions. Patients with a slow-disorganized background were older (3.05 [0.69, 9,14]) than those with a discontinuous or burst suppressed background: (0.08 [0.02, 2.59]), $p < 0.001$. Worse initial EEG Background Category was associated with longer CPR duration, more epinephrine doses administered

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during CA, higher lactate post-ROSC, absence of pupillary reactivity 24-hours post-ROSC, absence of stage 2 sleep architecture, and absence of EEG variability/reactivity.

Sixty-eight subjects (76%) had an unfavorable neurobehavioral outcome, including 30 subjects (34%) who did not survive to discharge. On univariate analyses, unfavorable neurobehavioral outcome was associated with unwitnessed CA, longer CPR duration, a cause of CA other than respiratory failure, disposition to places other than home, and gastrostomy-tube requirement (Supplemental Table 2). On univariate analyses, mortality was associated with longer CPR duration and higher lactate post-ROSC. Worse EEG Background Category, absence of stage 2 sleep architecture, and the absence of variability/reactivity were each associated with both unfavorable neurobehavioral outcome and mortality. Neither ES nor ESE were associated with unfavorable neurobehavioral outcome or mortality.

On multivariable analysis (statistically derived) (Table 1), worse initial EEG Background Category was associated with an increased odds for unfavorable neurobehavioral outcome (OR 4.37 [95%CI 1.38, 13.77], p=0.012; AUROC 0.87 [95%CI 0.77, 0.96]) and an increased odds for mortality (OR 6.93 [95%CI 2.36, 20.39], p=0.0004; AUROC 0.89 [95%CI 0.81, 0.96]).

For the clinically derived multi-modal prediction model, to maintain the most parsimonious model, we omitted CA location, cough, and stage 2 sleep architecture since these variables were correlated with other variables within each prediction category, and their addition did not enhance the predictive ability of the corresponding models (Supplemental Table 3). The most robust and parsimonious predictive model was the combination of Demographic/Arrest Variables [witnessed status, epinephrine doses, lactate] and EEG Background Category which achieved an AUROC for unfavorable neurobehavioral outcome of 0.90 (95%CI 0.83, 0,97) and an AUROC for mortality of 0.83 (95%CI 0.74, 0.93) (Table 2). Models containing EEG Background Category were superior to the same models without EEG. (Table 2).

There was no change in EEG Background Category from cEEG initiation to 12-hours post-ROSC in 82/87 subjects (94%), to 24-hours post-ROSC in 75/85 subjects (88%), to 36-hours post-ROSC in 57/73 subjects (78%), and to 48-hours post-ROSC in 43/57 subjects (75%). There was no association between worsening or improvement in EEG Background Category from the cEEG initiation to subsequent time points with neurobehavioral outcome or mortality (Table 3). Among subjects whose initial EEG Background Category was not attenuated-featureless (i.e., those whose EEG could worsen at future assessments), 0%-16.3% worsened from initial assessment at various future time points. All eight subjects with worsening EEG Background Category from cEEG initiation to 48-hours post-ROSC had an unfavorable outcome, including mortality in four subjects (Supplemental Table 4). Similarly, among subjects whose initial EEG Background Category was abnormal (i.e., those whose EEG could improve at future assessments), 6.4-12.9% improved from initial assessment at future time points. (Supplemental Table 4). Among subjects whose EEG Background Category improved from cEEG initiation to 48-hours post-ROSC, 5/6 (83.3%) survived to discharge but only 2/6 (33.3%) had a favorable neurobehavioral outcome.

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Discussion

In this single-center, prospective, observational study of multimodal monitoring to stratify outcomes in children resuscitated from CA, EEG background categories derived from full-montage conventional EEG using standardized terminology at standard time points post-ROSC were associated with short-term neurobehavioral outcome and mortality. The most robust and parsimonious predictive model included witnessed status, epinephrine doses, post-ROSC lactate, and EEG Background Category. It achieved an AUROC of 0.90 for unfavorable neurobehavioral outcome and an AUROC of 0.83 for mortality. These data expand the field by demonstrating that the addition of EEG Background Category to routinely utilized clinical and CA features enhances the ability to stratify brain injury severity. Changes in EEG Background Category from the initial EEG epoch were not associated with outcomes, highlighting the value of early EEG.

Using this cohort, we previously determined that early EEG background features predict neurobehavioral outcomes and mortality at discharge.[28] In that study, the optimal model incorporated EEG Background Category, stage 2 sleep architecture, and variability/reactivity. It had a specificity of 95% and 97% for unfavorable neurobehavioral outcome and mortality, respectively, yielding a positive predictive value of 86% for both unfavorable neurobehavioral outcome and mortality.[28] In the current study, we created the most parsimonious model that incorporated only data necessary to enhance prediction accuracy. Thus, although both EEG variability/reactivity and stage 2 sleep architecture were significantly associated with outcome, they were not included in the final model since they did not enhance the model's predictive accuracy. Further, these EEG features might be harder to assess since they might occur variably over time and could be impacted by administration of sedating medications.

More severe EEG background categories were associated with CA variables indicating more severe hypoxic-ischemic brain injury. Consistent with other studies, burst-suppression and attenuated-featureless EEG backgrounds were more common in patients with longer CPR duration, more epinephrine doses during resuscitation, higher lactate levels post-ROSC, and lack of pupillary reactivity 24 hours post-ROSC. Interestingly, other factors that are commonly associated with outcome such as CA location, witnessed/monitored status, and initial cardiac rhythm were not associated with more abnormal EEG background categories. These data highlight that EEG is a direct measure of brain function, whereas CA and resuscitation variables do not directly assess brain function. Thus, EEG may be able to discern early brain injury severity more accurately and objectively for individual patients.

We evaluated EEG data in a statistically derived multivariable data-based models and clinically-derived parsimonious prediction models which added EEG features to commonly used clinical variables. While neurobehavioral outcomes and mortality were each associated with different demographic/arrest variables, they were both associated with EEG Background Category. Other studies evaluating EEG background have utilized different covariates such as doses of epinephrine,[24] the use of dexmedetomidine and CPR duration,[26] or CT imaging and ammonia levels.[32] The model differences may be due to different variables analyzed at each study site, small cohorts, different statistical approaches, and the

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lack of uniform approaches to post-CA care. In our previous study, we found that clinical variables (CA location, initial rhythm, epinephrine doses, and witnessed CA status) had an AUROC of 0.74 for unfavorable neurobehavioral outcome, and incorporation of EEG background significantly improved the AUROC to 0.85 for unfavorable outcome.[24] In the current study, epinephrine doses, witnessed CA, and lactate post-ROSC had an AUC of 0.75 for unfavorable neurobehavioral outcome, and incorporation of EEG Background Category yielded a significantly improved AUROC of 0.90. The improvement in AUROC may reflect standardized EEG interpretation at specific times post-ROSC (rather than EEG data gleaned from reports only) or the addition of lactate post-ROSC (rather than CA location and initial rhythm). Our current data indicate that EEG Background Category improvement or worsening was not significantly associated with outcomes. Since patients in the normal category could not improve and patients in the attenuated category could not worsen, we performed sub-analyses excluding those subjects and found no significant associations with outcome. Similarly, a prior study of pediatric CA indicated that EEG changes (improvement or worsening) were not associated with outcome.[26] In our prior work using the same cohort, regression modeling indicated that EEG did not significantly change over time.[33] However, 8% to 30% of subjects changed over time.. Given that EEG changes only occur in 10-30% of patients,[33] this study was likely underpowered to assess associations of EEG background changes with outcome. Since EEG Background Category changes were not significantly associated with outcome, it is logical to incorporate early EEG within the first 12-hours of ROSC to stratify brain injury severity after CA. However, in rare patients who demonstrate improvement or worsening in EEG Background Category, incorporation of other predictive modalities may be particularly important.

ES occurred in seven subjects (8%). Recent studies report post-CA seizure rates of 10-47%.[24–26, 29, 30, 32] ES rates may appear to be decreasing over time due to more widespread use of cEEG, including among patients with less severe brain injury after CA, as recommended by recent consensus statements.[21–23] Alternatively, advances in resuscitation and post resuscitation care may have resulted in less secondary brain injury. The impact of ES on outcome is uncertain. In our prior study of 128 children after CA, ES were associated with unfavorable neurobehavioral outcomes at discharge but not with higher mortality.[24] In the current study, neither ES nor ESE were significantly associated with unfavorable outcome or mortality, likely due to small numbers. However, all seven subjects with ES, including six with ESE, had unfavorable neurobehavioral outcomes. Four of the seven subjects with ES, including three with ESE, died prior to discharge.

This study has several limitations. First, this was a single-center study with a robust cEEG program and standardized post-CA care. Therefore, the results may not be generalizable to other centers. Second, examination signs and lactate levels were missing for some patients who were therefore excluded from multivariable models. Third, clinicians were not blinded to study variable;. However, withdrawal of technological support did not occur during the initial 24 hours post-ROSC when all these variables were assessed. Fourth, we included subjects who were neurobehaviorally normal and abnormal prior to CA to enhance generalizability, but there may be differences in outcome predictors among patients with and without pre-existing neurobehavioral disorders. Finally, we evaluated a short-term gross outcome. Future studies would benefit from more standardized post-

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CA pathway-driven management, multi-center data collection, and longer-term and more detailed neurobehavioral and health-related quality-of-life outcome measures.

Early neuroimaging findings, serum biomarkers, CA features such as CA etiology and CPR duration, patient characteristics, and EEG are associated with outcomes, but they are insufficient alone. Multimodal approaches will enable clinicians more accurately stratify patients by brain injury severity early after pediatric CA. This study indicates that although more normal EEG features predict favorable outcome and more abnormal EEG features predict unfavorable outcomes, no EEG variable is perfectly accurate, consistent with prior studies.[11] Therapeutics targeting the post-CA syndrome,[8] including targeted temperature management, treatment of hypotension, avoidance of hyperoxia, achievement of normocarbia, and detection and treatment of seizures may improve outcomes. However, studies of therapeutic strategies have taken “a one size fits all” approach. Early stratification of patients by brain injury severity may allow clinicians to identify patients who could benefit from neuroprotective interventions in clinical trials and enable targeted interventional therapeutics based on individual patient characteristics.. Future prospective, large, and multi-center studies that use standardized EEG assessment and robust long-term outcomes are needed to better assess the ability of multi-modal models to stratify children by brain injury severity and perform accurate neuroprognostication.[8, 9, 11, 12, 48] However. early stratification should not be confused for early prognostication; stratification should guide early treatment decisions whereas prognostication should occur later and inform families and clinicians about outcomes. Clinicians need to be careful not use these data to prognosticate early to limit care which could perpetuate a self-fulfilling prophecy.

Conclusion:

The addition of standardized EEG Background Categories to readily available CA variables significantly improved the early stratification of brain injury severity after pediatric CA.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Statistically Derived Multivariable Models of Outcomes.

Unfavorable Neurobehavioral Outcome (Observations used =78)		
	OR (95%CI)	**p-value**
One unit increase in initial EEG Background Category	4.37 (1.38, 13.77)	0.012
Pre-arrest ventilation		
Yes	Reference	
No	1.96 (0.41, 9.48)	0.4022
Arrest witnessed		
Yes	Reference	
No	3.83 (0.48, 30.94)	0.2074
Arrest cause of respiratory failure		
Yes	Reference	
No	2.01 (0.48, 8.50)	0.3410
Epinephrine doses		
0-1 dose	Reference	
2-4 doses vs.	0.45 (0.09, 2.17)	0.3213
≥5 doses	0.03 (0.002, 0.37)	0.0069
Pupils reactive at 24 hours		
Yes	Reference	
No	2.49 (0.43, 14.48)	0.3107
Mortality (observations used=71)		
	OR (95%CI)	**p-value**
One unit increase in initial EEG Background Category	6.93 (2.36, 20.39)	0.0004
Pre-arrest congenital heart disease		
No	Reference	
Yes	3.68 (0.59, 22.78)	0.161
Pre-arrest vasoactive infusion		
Yes	Reference	
No	1.41 (0.15, 13.17)	0.761
Epinephrine doses		
0-1 dose	Reference	
2-4 doses	0.97 (0.15, 6.24)	0.97
≥5 doses	0.34 (0.02, 7.57)	0.50
One mmol/L increase in initial lactate	1.06 (0.90, 1.25)	0.47
Pupillary Reactive at 24 Hours		
Yes	Reference	
No	1.20 (0.24, 5.95)	0.82
Neuromuscular diagnosis		

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Unfavorable Neurobehavioral Outcome (Observations used =78)		
	OR (95%CI)	**p-value**
No	Reference	
Yes	12.67 (1.47, 108.98)	0.021

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Table 2.

Comparing area under the receiver operating characteristic curves (AUROC) between models based combinations of Demographics/Arrest Variables (witnessed status, doses of epinephrine, initial lactate), Examination Signs (gag, pupillary reactivity), and EEG Features (initial EEG Background Category).

Model Components	Unfavorable Neurobehavioral Outcome			Mortality		
	Observations	AUROC (95%CI)	p-value	Observations	AUROC (95%CI)	p-value
Demographic/Arrest + Examination	66	0.83 (0.71, 0.94)	Ref	66	0.73 (0.60, 0.86)	Ref
Demographic/Arrest	66	0.75 (0.64, 0.87)	0.2782	66	0.66 (0.51, 0.81)	0.1829
Examination	66	0.62 (0.49, 0.74)	0.0113	66	0.68 (0.56, 0.80)	0.4145
Demographics/Arrest + EEG	82	0.90 (0.83, 0.97)	Ref	82	0.83 (0.74, 0.93)	Ref
Demographic/Arrest	82	0.75 (0.64, 0.85)	0.009	82	0.69 (0.56, 0.81)	0.0141
EEG	82	0.76 (0.67, 0.87)	0.005	82	0.82 (0.73, 0.91)	0.4788
Examination + EEG	72	0.74 (0.60, 0.88)	Ref	72	0.80 (0.68, 0.93)	Ref
Examination	72	0.59 (0.47, 0.72)	0.0535	72	0.67 (0.55, 0.79)	0.0114
EEG	72	0.71 (0.58, 0.83)	0.2414	72	0.78 (0.66, 0.90)	0.2553
Demographic/Arrest + Examination + EEG	66	0.93 (0.87, 1.00)	Ref	66	0.85 (0.75, 0.95)	Ref
Demographic/Arrest + Examination	66	0.83 (0.71, 0.94)	0.0261	66	0.73 (0.60, 0.86)	0.0391
Demographic/Arrest + EEG	66	0.91 (0.85, 0.98)	0.3686	66	0.83 (0.71, 0.94)	0.32
Examination + EEG	66	0.81 (0.69, 0.94)	0.0444	66	0.84 (0.73, 0.95)	0.6009
Statistically derived Clinically-Derived multivariable model [a]	66	0.92 (0.86, 0.99)	0.6360	66	0.88 (0.80, 0.97)	0.3821

[a] Variables used in statistically derived multivariable models are different for unfavorable neurobehavioral outcome and mortality.

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Table 3.

Associations of change in EEG Background Category between epochs with outcomes.

	Overall	Neurobehavioral Outcome			Mortality		
		Unfavorable (n=68)	Favorable (n=21)	P-value	Died (n=30)	Survived (n=59)	p-value
Initial EEG (N=89)							
Normal	9 (10.1%)	3 (33.3%)	6 (66.7%)	0.0031	1 (11.1%)	8 (88.9%)	<0.0001
Slow-Disorganized	44 (49.4%)	33 (75%)	11 (25%)		7 (15.9%)	37 (84.1%)	
Discontinuous or Burst-Suppression	22 (24.7%)	18 (81.8%)	4 (18.2%)		10 (45.5%)	12 (54.6%)	
Attenuated-Featureless	14 (15.7%)	14 (100%)	0 (0)		12 (85.7%)	2 (14.3%)	
Change score from initial to 12-hours (N=87)							
No change (0)	82 (94.3%)	63 (76.8%)	19 (23.2%)	0.5904	27 (32.9%)	55 (67.1%)	1
Improved (−1)	5 (5.7%)	3 (60.0%)	2 (40.0%)		2 (40.0%)	3 (60.0%)	
Change score from initial to 24-hours (N=85)							
Worsened (1)	3 (3.5%)	2 (66.7%)	1 (33.3%)	0.3638	1 (33.3%)	2 (66.7%)	1
No change (0)	75 (88.2%)	59 (78.7%)	16 (21.3%)		26 (34.7%)	49 (65.3%)	
Improved (−1)	7 (8.2%)	4 (57.1%)	3 (42.9%)		2 (28.6%)	5 (71.4%)	
Change score from initial to 36-hours (N=73)							
Worsened (2)	1 (1.4%)	1 (100%)	0 (0)	0.6699	1 (100%)	0 (0)	0.551
Worsened (1)	6 (8.2%)	5 (83.3%)	1 (16.7%)		2 (33.3%)	4 (66.7%)	
No change (0)	57 (78.1%)	46 (80.7%)	11 (19.3%)		19 (33.3%)	38 (66.7%)	
Improved (−1)	9 (12.3%)	6 (66.7%)	3 (33.3%)		2 (22.2%)	7 (77.8%)	
Change score from initial to 48-hours (N=57)							
Worsened (2)	1 (1.8%)	1 (100%)	0 (0)	0.4463	1 (100%)	0 (0)	0.4919
Worsened (1)	7 (12.3%)	7 (100%)	0 (0)		3 (42.9%)	4 (57.1%)	
No change (0)	43 (75.4%)	35 (81.4%)	8 (18.6%)		16 (37.2%)	27 (62.8%)	
Improved (−1)	6 (10.5%)	4 (66.7%)	2 (33.3%)		1 (16.7%)	5 (83.3%)	