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Clinical paper

Association of EEG characteristics with outcomes following pediatric ICU cardiac arrest: A secondary analysis of the ICU-RESUScitation trial

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Abstract

Background and Objectives: There are limited tools available following cardiac arrest to prognosticate neurologic outcomes. Prior retrospective and single center studies have demonstrated early EEG features are associated with neurologic outcome. This study aimed to evaluate the prognostic value of EEG for pediatric in-hospital cardiac arrest (IHCA) in a prospective, multicenter study.

Methods: This cohort study is a secondary analysis of the ICU-Resuscitation trial, a multicenter randomized interventional trial conducted at 18 pediatric and pediatric cardiac ICUs in the United States. Patients who achieved return of circulation (ROC) and had post-ROC EEG monitoring were eligible for inclusion. Patients < 90 days old and those with pre-arrest Pediatric Cerebral Performance Category (PCPC) scores > 3 were excluded. EEG features of interest included EEG Background Category, and presence of focal abnormalities, sleep spindles, variability, reactivity, periodic and rhythmic patterns, and seizures. The primary outcome was survival to hospital discharge with favorable neurologic outcome. Associations between EEG features and outcomes were assessed with multivariable logistic regression. Prediction models with and without EEG Background Category were developed and receiver operator characteristic curves compared.

Results: Of the 1129 patients with an index cardiac arrest who achieved ROC in the parent study, 261 had EEG within 24 h of ROC, of which 151 were evaluable. The cohort included 57% males with a median age of 1.1 years (IQR 0.4, 6.8). EEG features including EEG Background Category, sleep spindles, variability, and reactivity were associated with survival with favorable outcome and survival, (all $p < 0.001$). The addition of EEG Background Category to clinical models including age category, illness category, PRISM score, duration of CPR, first documented rhythm, highest early post-arrest arterial lactate improved the prediction accuracy achieving an AUROC of 0.84 (CI 0.77–0.92), compared to AUROC of 0.76 (CI 0.67–0.85) ($p = 0.005$) without EEG Background Category.

Conclusion: This multicenter study demonstrates the value of EEG, in the first 24 h following ROC, for predicting survival with favorable outcome after a pediatric IHCA.

Keywords: Cardiac arrest, Pediatric cardiac arrest, Post-resuscitation care, Neuro-prognostication, Electroencephalography

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Introduction

More than 15,000 children per year experience an in-hospital cardiac arrest (IHCA) in the United States, and 40–50% survive to hospital discharge with a favorable neurologic outcome.[1–4] Medical providers have few reliable biomarkers to predict outcomes.[5] The American Heart Association (AHA) guidelines recommend electroencephalographic (EEG) monitoring in the first week post-arrest as one factor for prognostication.[6] Worse neurologic outcomes are associated with early EEG features including background attenuation, lack of variability and reactivity, presence of seizures, and lack of sleep architecture.[7–11] Further, adding EEG features to patient and arrest characteristics increases accuracy for predicting neurologic outcome.[11]. To date, there are no multicenter studies evaluating the predictive accuracy of EEG features with outcomes after pediatric cardiac arrest.

We performed a secondary analysis of data acquired in a prospective multicenter study of IHCA to determine whether EEG features during the first 24 h following cardiac arrest are associated with neurologic outcome and survival to hospital discharge. We hypothesized that the addition of early EEG features to patient and arrest characteristics would increase predictive accuracy of survival with favorable neurologic outcome and survival to hospital discharge compared to patient and arrest characteristics alone.[12–16]

Material and methods

This study was as a secondary analysis of the ICU-Resuscitation trial (ICU-RESUS; NCT02837497), a parallel stepped-wedge hybrid cluster randomized trial conducted at 18 pediatric and cardiac ICUs at 10 sites in the United States between October 1, 2016, and March 31, 2021. The methods[17] and primary results[18] have been published. The study included children 37 weeks post-conception to 18 years old IHCA requiring compressions during an ICU admission. Children were excluded if they had a pre-existing terminal illness and/or were not expected to survive to discharge prior to IHCA, were not being treated with aggressive ICU therapies, were diagnosed with brain death, or had an associated out-of-hospital cardiac arrest. The intervention included a two-part ICU resuscitation quality improvement bundle of point-of-care CPR training on a manikin and structured cardiac arrest debriefs. The primary outcome was survival to hospital discharge with favorable neurologic outcome, defined as Pediatric Cerebral Performance (PCPC)[19] score of 1 to 3 or no change from baseline. PCPC is a validated six-point scale that categorizes functional impairment (1 = normal, 2 = mild disability, 3 = moderate disability, 4 = severe disability, 5 = coma and vegetative state, and 6 = death).[19] The secondary outcome was survival to hospital discharge.

Data elements collected for the ICU-RESUS trial included patient demographics, arrest characteristics, and post-cardiac arrest care data per standard Utstein-style reporting.[17] Pediatric Risk of Mortality (PRISM) III score[20] was assessed 2–6 h prior to cardiac arrest. EEG reports during the first 24 h post cardiac arrest were collected if EEG was clinically obtained.

Standard protocol approvals, registrations, and patient consents

The University of Utah central institutional review board approved the project. Pediatric patients with cardiac arrest and ICU clinicians were enrolled under a waiver of consent.

EEG study

All patients from the *ICU-RESUS* trial were eligible for this study. We excluded patients who did not have an EEG within 24 h of return of circulation, patients with a pre-arrest PCPC score of 4 or 5 because they were very likely to have abnormal EEG backgrounds at baseline,[21–24] and patients < 90 days old because discontinuous EEG background in neonates may be normal rather than indicative of brain injury observed post-arrest.[25]

Clinical EEG reports were generated by pediatric electroencephalographers at each site using standardized American Clinical Neurophysiology Society (ACNS) terminology. Key features from EEG reports performed during the 24 h following ROC were extracted by three neurologists (N.S.A., C.A.P., and E.M.) using a standardized form based on terminology from the ACNS.[26] An initial set of ten EEGs was scored by N.S.A. and C.A.P. to create a consensus document for scoring. EEG Background Category was scored as normal, slow-disorganized (abnormal but continuous), discontinuous/burst suppression (50–99% recording with attenuation or suppression), or attenuated (no voltages > 10uV), as used in prior critical care EEG studies.[9,27–32] Other EEG features including focal abnormalities, sleep spindles, variability, reactivity, periodic and rhythmic patterns, and seizures, were scored as “present”, “absent”, or “unknown.” Sleep spindles were scored as “present” if reported as present in any form, including asymmetric, early, or primitive. Reports listing “possible spindles” were scored as absent. Variability was scored as “present” if reported specifically or if there was a description of state change, and it was scored as “absent” if the EEG was noted to lack state change or to be monotonous. Reactivity was scored as “present” or “absent” only if specifically stated. Periodic and rhythmic patterns were recorded as “present” if identified in the report, and they were classified by location (lateralized, generalized, bilateral independent, or multifocal) and morphology (periodic discharges, rhythmic delta activity, or spike wave discharges). Seizures were scored as “present” if noted in the clinical report or if the report described features which met seizure criteria from the American Clinical Neurophysiology Society..[26] Electroencephalographic status epilepticus was defined as $\geq$ 50% of a one-hour epoch containing electroencephalographic seizures. These definitions are consistent with prior critical care EEG studies[27,30,31] and published definitions.[33]

The primary outcome was survival to hospital discharge with favorable outcome and the secondary outcome was survival to hospital discharge.

Continuous variables were summarized as median [interquartile ranges], and categorical variables were presented as frequencies and percentages. Demographic and clinical characteristics were compared across EEG Background Categories. The association between EEG Background Category and demographic characteristics, clinical characteristics, and CPR quality measures were evaluated with the Cochrane-Armitage trend test for binary variables, the Kruskal-Wallis test for other nominal variables, and the Jonckheere-Terpstra test for ordinal variables. These tests were chosen to account for the ordinal nature of the severity of EEG Background Category. The association of clinical and EEG characteristics with outcomes were assessed using Fisher’s exact test for nominal variables and the Wilcoxon rank-sum test for ordinal variables. We performed a post-hoc analysis in which EEG Background Category was simplified to two categories: continuous (normal or slow-disorganized) vs. discontinuous/attenuated (discontinuous, burst suppression, or attenuated).

Multivariable Poisson regression models with robust error estimation were used to determine the association between EEG features and outcomes adjusting for age category, illness category (medical cardiac, surgical cardiac, medical non-cardiac, surgical non-cardiac), CPR time (weekday vs. night/weekend), CPR duration, first documented rhythm, highest arterial lactate (0–6 h after ROC) and PRISM score as *a priori* covariates.[18,34–39] EEG Background Category was represented numerically with increasing values for more abnormal EEG Background Category (normal = 1, slow/disorganized = 2, discontinuous/burst suppression = 3, attenuated = 4). To avoid overfitting and numeric instability with model convergence, only features reported in > 10 patients were included in the multivariable analysis. Stepwise selection was used to find a parsimonious model of clinical and EEG features, in which the *a priori* variables were forced into the model and the candidate variables included the EEG features. The final models for the primary and secondary outcome were reported with adjusted relative risk ratios, associated 95% confidence intervals, and p-values. A receiver operator characteristic curve was created to determine the area under the curve (AUC) for the final model. SAS software (version 9.4; SAS Institute Inc) was used for the statistical analyses.

Results

Among 1129 index events in the ICU-RESUS trial, 261 (24%) underwent EEG monitoring within 24 h after ROC. After applying exclusion criteria, 151 patients were included (Fig. 1). The cohort included 86 males (57%), and the median age was 1.1 years (IQR 0.4, 6.8) (Table 1). EEG Background Category in the 24 h following arrest was classified as normal in 25 (16%), slow/disorganized in 98 (65%), discontinuous/burst suppression in 16 (11%), and attenuated in 12 (8%) patients. None of the demographic variables assessed were associated with EEG Background Category. Shorter duration of CPR ($p < 0.001$), absence of pre-arrest vasoactive infusions ($p = 0.005$), fewer number of epinephrine boluses ($p < 0.001$), lower early post-arrest arterial lactate ($p < 0.001$), and higher early post-arrest arterial pH ($p < 0.001$) were associated with more normal EEG Background Category (Table 1).

Eighty-six patients (57%) survived with favorable outcome, and 97 (64%) patients survived to hospital discharge. Several characteristics were associated with outcomes of interest (Table 2). Survival with favorable outcome was associated with illness category ($p = 0.014$), shorter duration of CPR ($p = 0.002$), lower number of epinephrine boluses ($p = 0.006$), lower post-arrest peak arterial lactate ($p = 0.002$), higher early post-arrest arterial pH ($p = 0.002$), and absence of mechanical ventilation prior to arrest ($p = 0.029$).

EEG Background Category distribution was associated with survival with favorable outcome and survival to hospital discharge (both $p < 0.001$). Survival with favorable outcome occurred in 21/25 (84%) of patients with a normal background and 64/98 (65%) with a slow/disorganized background but only 1/16 (6%) with a discontinuous/burst suppression background and 0/12 (0%) with an attenuated background. Similarly, survival to hospital discharge occurred in 23/25 (96%) with a normal background and 69/98 (70%) with a slow/disorganized background but only 4/16 (25%) with a discontinuous/burst suppression background and 1/11 (9%) with an attenuated background survived to hospital discharge. The presence of sleep spindles, variability, and reactivity were associated with survival with favorable outcome and survival to hospital discharge (all $p < 0.001$). Data could not be derived for focal abnormalities in 3/151 (2%), reactivity in 60/151 (40%), variability in 31/151 (21%), periodic and rhythmic patterns in 6/151 (4%), and seizures in 1/151 (1%). The absence of focal abnormalities ($p = 0.026$) and EEG seizures ($p = 0.021$) were associated with survival with favorable outcome but not survival to hospital to discharge.

In a multivariable model adjusted for age category, illness category, PRISM score, duration of CPR, first documented rhythm, and highest early post-arrest arterial lactate, for each worsening EEG Background Category there was an incrementally lower likelihood of survival with favorable outcome (aRR 0.46 [0.35–0.61]) and survival to hospital discharge (aRR 0.53 [0.41, 0.69]) (Table 3).

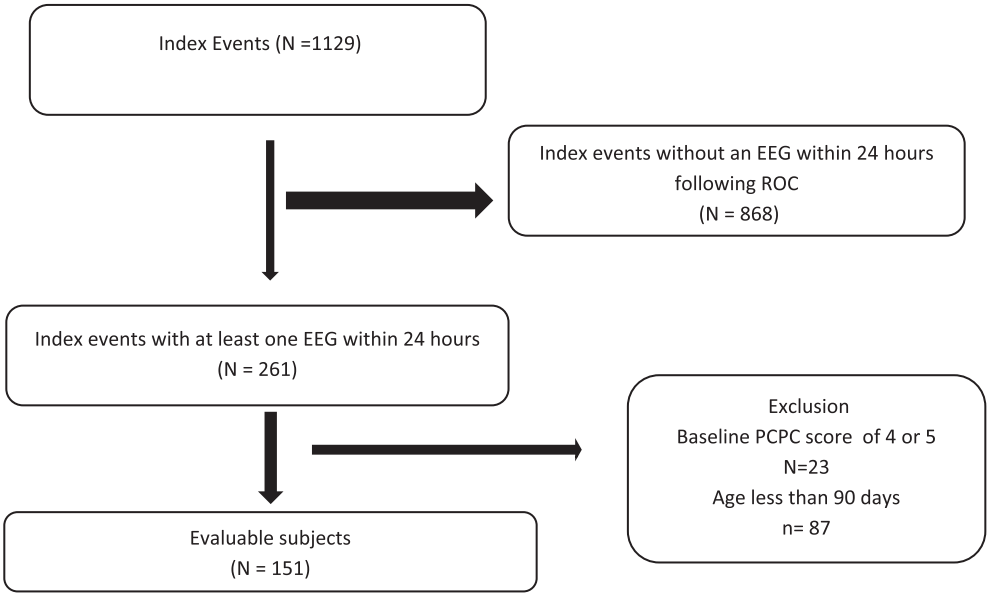

Fig. 1 – CONSORT Diagram outlining patient inclusion and exclusion.

Table 1 – Clinical characteristics by 24-hour post-arrest EEG background category.

EEG Background Category	Overall (N = 151)	Normal (N = 25)	Slow/Disorganized (N = 98)	Discontinuous/Burst Suppression(N = 16)	Attenuated (N = 12)	P-value
DEMOGRAPHIC CHARACTERISTICS						
Age (years)	1.1 [0.4,6.8]	0.5 [0.3,1.1]	1.6 [0.5,9.6]	0.6 [0.5,2.6]	0.4 [0.3,2.2]	0.696[1]
Age						0.873[2]
≤ 1 year	73 (48.3%)	18 (72.0%)	37 (37.8%)	10 (62.5%)	8 (66.7%)	
> 1 year	78 (51.7%)	7 (28.0%)	61 (62.2%)	6 (37.5%)	4 (33.3%)	
Male	86 (57.0%)	11 (44.0%)	57 (58.2%)	12 (75.0%)	6 (50.0%)	0.336[2]
Race						0.178[3]
White	66 (43.7%)	8 (32.0%)	45 (45.9%)	8 (50.0%)	5 (41.7%)	
Black or African American	37 (24.5%)	6 (24.0%)	25 (25.5%)	1 (6.3%)	5 (41.7%)	
Other	11 (7.3%)	4 (16.0%)	6 (6.1%)	1 (6.3%)	0 (0.0%)	
Unknown or Not Reported	37 (24.5%)	7 (28.0%)	22 (22.4%)	6 (37.5%)	2 (16.7%)	
Preexisting medical conditions						
Respiratory insufficiency	132 (87.4%)	22 (88.0%)	86 (87.8%)	13 (81.3%)	11 (91.7%)	0.971[2]
Hypotension	101 (66.9%)	11 (44.0%)	70 (71.4%)	11 (68.8%)	9 (75.0%)	0.070[2]
Congestive heart failure	25 (16.6%)	2 (8.0%)	16 (16.3%)	6 (37.5%)	1 (8.3%)	0.312[2]
Pneumonia	24 (15.9%)	7 (28.0%)	11 (11.2%)	3 (18.8%)	3 (25.0%)	0.911[2]
Sepsis	21 (13.9%)	2 (8.0%)	16 (16.3%)	2 (12.5%)	1 (8.3%)	0.979[2]
Trauma	2 (1.3%)	0 (0.0%)	2 (2.0%)	0 (0.0%)	0 (0.0%)	0.853[2]
Renal insufficiency	16 (10.6%)	1 (4.0%)	13 (13.3%)	2 (12.5%)	0 (0.0%)	0.838[2]
Malignancy	8 (5.3%)	1 (4.0%)	5 (5.1%)	1 (6.3%)	1 (8.3%)	0.565[2]
Pulmonary hypertension	31 (20.5%)	9 (36.0%)	18 (18.4%)	2 (12.5%)	2 (16.7%)	0.108[2]
EVENT CHARACTERISTICS						
Duration of CPR (minutes)	10.0 [4.0,33.0]	5.0 [3.0,10.0]	10.0 [4.0,26.0]	33.0 [15.0,40.5]	41.5 [7.5,56.5]	<.001[1]
Illness category						0.359[3]
Medical cardiac	45 (29.8%)	7 (28.0%)	25 (25.5%)	5 (31.3%)	8 (66.7%)	
Medical non-cardiac	54 (35.8%)	9 (36.0%)	36 (36.7%)	6 (37.5%)	3 (25.0%)	
Surgical cardiac	46 (30.5%)	8 (32.0%)	33 (33.7%)	4 (25.0%)	1 (8.3%)	
Surgical non-cardiac	6 (4.0%)	1 (4.0%)	4 (4.1%)	1 (6.3%)	0 (0.0%)	
Trauma	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Interventions in place						
ECMO	2 (1.3%)	0 (0.0%)	2 (2.0%)	0 (0.0%)	0 (0.0%)	0.853[2]
Vascular access	143 (94.7%)	23 (92.0%)	93 (94.9%)	16 (100.0%)	11 (91.7%)	0.704[2]
Arterial catheter	77 (51.0%)	10 (40.0%)	53 (54.1%)	6 (37.5%)	8 (66.7%)	0.352[2]
Central venous catheter	100 (66.2%)	14 (56.0%)	64 (65.3%)	14 (87.5%)	8 (66.7%)	0.170[2]
Vasoactive infusion	81 (53.6%)	7 (28.0%)	55 (56.1%)	10 (62.5%)	9 (75.0%)	0.005[2]
Invasive mechanical ventilation	94 (62.3%)	16 (64.0%)	58 (59.2%)	11 (68.8%)	9 (75.0%)	0.419[2]
Non-invasive ventilation	29 (19.2%)	2 (8.0%)	22 (22.4%)	2 (12.5%)	3 (25.0%)	0.397[2]
Immediate cause of arrest						
Arrhythmia	28 (18.5%)	4 (16.0%)	18 (18.4%)	4 (25.0%)	2 (16.7%)	0.738[2]
Cyanosis without respiratory decompensation	7 (4.6%)	4 (16.0%)	2 (2.0%)	0 (0.0%)	1 (8.3%)	0.171[2]
Hypotension	85 (56.3%)	11 (44.0%)	58 (59.2%)	8 (50.0%)	8 (66.7%)	0.326[2]
Respiratory decompensation	85 (56.3%)	12 (48.0%)	61 (62.2%)	7 (43.8%)	5 (41.7%)	0.458[2]
First documented rhythm						0.859[3]
Pulseless electrical activity / asystole	72 (47.7%)	8 (32.0%)	53 (54.1%)	4 (25.0%)	7 (58.3%)	
Ventricular fibrillation / tachycardia	13 (8.6%)	2 (8.0%)	9 (9.2%)	1 (6.3%)	1 (8.3%)	
Bradycardia with poor perfusion	66 (43.7%)	15 (60.0%)	36 (36.7%)	11 (68.8%)	4 (33.3%)	
Pharmacologic measurements						

Table 1 (continued)

EEG Background Category						
	Overall (N = 151)	Normal (N = 25)	Slow/Disorganized (N = 98)	Discontinuous/Burst Suppression(N = 16)	Attenuated (N = 12)	P-value
Epinephrine	139 (92.1%)	20 (80.0%)	92 (93.9%)	16 (100.0%)	11 (91.7%)	0.098[2]
Number of epinephrine boluses	3.00 [2.00,7.00]	2.00 [1.00,3.00]	3.00 [1.00,5.50]	7.50 [4.00,12.00]	9.00 [2.00,16.00]	<.001[1]
Highest arterial lactate (0–6 h after)	8.70 [3.90,14.50]	2.60 [1.60,3.70]	7.21 [4.06,13.75]	14.70 [13.56,19.34]	16.00 [11.48,19.22]	<.001[1]
Lowest arterial pH (0–6 h post-arrest)	7.21 [7.06,7.31]	7.32 [7.17,7.38]	7.24 [7.09,7.31]	7.10 [6.91,7.29]	7.05 [7.01,7.14]	<.001[1]

ECMO = ExtraCorporeal Membrane Oxygenation.
[1] Jonckheere-Terpstra Test.
[2] Cochran-Armitage trend test.
[3] Kruskal-Wallis Test.

The presence of sleep spindles, variability, or reactivity were all associated with increased survival with favorable outcome and survival to hospital discharge (Table 3).

A stepwise selected multivariable regression including age category, illness category, PRISM score, duration of CPR, first documented rhythm, highest early post-arrest arterial lactate, and EEG Background Category (numeric) was used to create the most parsimonious model of survival with favorable outcome using clinical and post-arrest EEG features.[6,18] EEG Background Category increased accuracy of the model beyond the included *a priori* clinical features. The overall model had an AUC of 0.84 (CI 0.77–0.92), compared to an AUC of 0.76 (CI 0.67–0.85) (p = 0.005) in a model without EEG Background Category (Table 4) (Fig. 2). Other EEG features (spindles, reactivity, variability) did not increase model accuracy after the inclusion of EEG Background Category.

In a post-hoc analysis of outcomes, EEG Background Category was dichotomized as continuous (normal/slow/disorganized) (123; 81%) vs discontinuous-attenuated (28; 19%) to consolidate categories with small numbers (eTable 1). Patients with a continuous EEG Background Category were more likely to survive with favorable outcome compared to those with discontinuous/attenuated EEG Background Category (69% vs. 4%, p < 0.001). Only one patient (1/28; 4%) with a discontinuous/attenuated EEG Background Category survived with favorable outcome. Patients with a continuous EEG Background Category who survived with favorable outcome were less likely to have pre-existing renal insufficiency (p = 0.033) and pre-arrest invasive mechanical ventilation (p = 0.048) than those who survived with an unfavorable outcome. They also had less baseline disability (p = 0.007), higher post-arrest arterial pH (p = 0.021), and lower PRISM score 2–6 h prior to CPR (p = 0.019). Additionally, these patients were more likely to have EEG variability (p = 0.002) and reactivity (p < 0.001). Finally, the time to death from ROC was shorter in patients with discontinuous/attenuated EEG Background Category than continuous EEG Background Category (4.75 [2.12–19.15] vs 15.75 [5.28–53.38]) with the majority occurring within 7 days (52% vs. 26%).

Discussion

This multicenter, prospective study of children without pre-existing moderate or severe disability at baseline found that EEG features in the first 24 h after an IHCA were associated with survival with favorable outcome and survival to hospital discharge. Inclusion of EEG Background Category, sleep spindles, variability, and reactivity increased the accuracy of prediction models compared to models derived from clinical variables alone. The severity of the EEG Background Category abnormality was the strongest predictor of outcome in a model that included key clinical characteristics and post-arrest measures.

EEG background activity is a measure of cerebral function, and rapid changes occur in response to decreased cerebral perfusion, hypoxemia, increased intracranial pressure, and focal injury.[40] Inadequate perfusion may alter EEG background causing slowing (loss of faster frequencies) and loss of normal waveform organization; subsequent return of normal perfusion and oxygen delivery results in EEG normalization.[41] Severe brain injury results in more substantial EEG changes, including discontinuity (including burst suppression) and ultimately an attenuated or featureless EEG. These changes suggest permanent injury.[42–46] EEG background category is collinear with EEG reactivity, variability, and sleep architecture. Though the EEG features of variability and reactivity had high percent of "unknowns", we suspect that an unreported feature is more likely to reflect its' absence, given the strong relationship between the presence of these features with EEG background. This study differs from previous EEG studies in children following cardiac arrest in several ways. First, it is the largest multicenter study evaluating the prognostic value of EEG. Second, the study demonstrates that not only does inclusion of EEG Background Category increase the accuracy of prediction models, but EEG Background Category outperforms traditional markers of outcome including illness category, PRISM score, highest lactate, first documented rhythm, and CPR duration. Third, survival with favorable outcome (57%) in this cohort was higher than most prior studies which estimate survival between 38–49%.[1–4] Multiple factors may contribute, including assessment of patients from an interventional trial focused on improving outcome from IHCA such that patients tended to receive high quality care, exclusion of patients not expected to survive to hospital discharge prior to IHCA, and exclusion of patients with moderate to severe baseline disability. The high proportion of survivors with favorable outcomes may have limited our ability to detect stronger associations between EEG variables and unfavorable outcome.

Our results are consistent with prior single center cohorts, including patients with both in- and out-of-hospital cardiac arrests.[8–11,47] A

Table 2 – Clinical and EEG characteristics by outcome.

		Survival to hospital discharge with favorable outcome			Survival to hospital discharge		
	Overall (N = 151)	No(N = 65)	Yes(N = 86)	P-value	No(N = 54)	Yes(N = 97)	P-value
DEMOGRAPHIC CHARACTERISTICS							
Age				0.254[1]			1.000[1]
≤ 1 year	73 (48.3%)	35 (53.8%)	38 (44.2%)		26 (48.1%)	47 (48.5%)	
> 1 year	78 (51.7%)	30 (46.2%)	48 (55.8%)		28 (51.9%)	50 (51.5%)	
Male	86 (57.0%)	37 (56.9%)	49 (57.0%)	1.000[1]	30 (55.6%)	56 (57.7%)	0.864[1]
Race				0.564[1]			0.957[1]
White	66 (43.7%)	32 (49.2%)	34 (39.5%)		25 (46.3%)	41 (42.3%)	
Black or African American	37 (24.5%)	14 (21.5%)	23 (26.7%)		13 (24.1%)	24 (24.7%)	
Other	11 (7.3%)	5 (7.7%)	6 (7.0%)		4 (7.4%)	7 (7.2%)	
Unknown or Not Reported	37 (24.5%)	14 (21.5%)	23 (26.7%)		12 (22.2%)	25 (25.8%)	
Preexisting medical conditions							
Respiratory insufficiency	132 (87.4%)	59 (90.8%)	73 (84.9%)	0.329[1]	49 (90.7%)	83 (85.6%)	0.448[1]
Hypotension	101 (66.9%)	48 (73.8%)	53 (61.6%)	0.121[1]	43 (79.6%)	58 (59.8%)	0.018[1]
Congestive heart failure	25 (16.6%)	13 (20.0%)	12 (14.0%)	0.379[1]	13 (24.1%)	12 (12.4%)	0.072[1]
Pneumonia	24 (15.9%)	11 (16.9%)	13 (15.1%)	0.824[1]	8 (14.8%)	16 (16.5%)	1.000[1]
Sepsis	21 (13.9%)	11 (16.9%)	10 (11.6%)	0.477[1]	8 (14.8%)	13 (13.4%)	0.810[1]
Trauma	2 (1.3%)	0 (0.0%)	2 (2.3%)	0.506[1]	0 (0.0%)	2 (2.1%)	0.537[1]
Renal insufficiency	16 (10.6%)	10 (15.4%)	6 (7.0%)	0.114[1]	9 (16.7%)	7 (7.2%)	0.097[1]
Malignancy	8 (5.3%)	5 (7.7%)	3 (3.5%)	0.291[1]	5 (9.3%)	3 (3.1%)	0.135[1]
Pulmonary hypertension	31 (20.5%)	10 (15.4%)	21 (24.4%)	0.223[1]	7 (13.0%)	24 (24.7%)	0.097[1]
EVENT CHARACTERISTICS							
Duration of CPR (minutes)	10.0 [4.0,33.0]	19.0 [6.0,38.0]	7.5 [3.0,23.0]	0.007[2]	23.0 [6.0,43.0]	8.0 [3.0,23.0]	0.002[2]
Illness category				0.014[1]			0.010[1]
Medical cardiac	45 (29.8%)	28 (43.1%)	17 (19.8%)		25 (46.3%)	20 (20.6%)	
Medical non-cardiac	54 (35.8%)	21 (32.3%)	33 (38.4%)		16 (29.6%)	38 (39.2%)	
Surgical cardiac	46 (30.5%)	14 (21.5%)	32 (37.2%)		11 (20.4%)	35 (36.1%)	
Surgical non-cardiac	6 (4.0%)	2 (3.1%)	4 (4.7%)		2 (3.7%)	4 (4.1%)	
Interventions in place							
ECMO	2 (1.3%)	1 (1.5%)	1 (1.2%)	1.000[1]	1 (1.9%)	1 (1.0%)	1.000[1]
Vascular access	143 (94.7%)	62 (95.4%)	81 (94.2%)	1.000[1]	52 (96.3%)	91 (93.8%)	0.712[1]
Arterial catheter	77 (51.0%)	36 (55.4%)	41 (47.7%)	0.412[1]	32 (59.3%)	45 (46.4%)	0.174[1]
Central venous catheter	100 (66.2%)	48 (73.8%)	52 (60.5%)	0.117[1]	41 (75.9%)	59 (60.8%)	0.073[1]
Vasoactive infusion	81 (53.6%)	40 (61.5%)	41 (47.7%)	0.102[1]	36 (66.7%)	45 (46.4%)	0.018[1]
Invasive mechanical ventilation	94 (62.3%)	47 (72.3%)	47 (54.7%)	0.029[1]	39 (72.2%)	55 (56.7%)	0.080[1]
Non-invasive ventilation	29 (19.2%)	14 (21.5%)	15 (17.4%)	0.539[1]	11 (20.4%)	18 (18.6%)	0.831[1]
Immediate cause of arrest							
Arrhythmia	28 (18.5%)	12 (18.5%)	16 (18.6%)	1.000[1]	11 (20.4%)	17 (17.5%)	0.668[1]
Cyanosis without respiratory decompensation	7 (4.6%)	3 (4.6%)	4 (4.7%)	1.000[1]	1 (1.9%)	6 (6.2%)	0.422[1]
Hypotension	85 (56.3%)	40 (61.5%)	45 (52.3%)	0.320[1]	35 (64.8%)	50 (51.5%)	0.127[1]
Respiratory decompensation	85 (56.3%)	34 (52.3%)	51 (59.3%)	0.412[1]	29 (53.7%)	56 (57.7%)	0.732[1]
First documented rhythm				0.802[1]			0.740[1]
Pulseless electrical activity / asystole	72 (47.7%)	29 (44.6%)	43 (50.0%)		25 (46.3%)	47 (48.5%)	
Ventricular fibrillation / tachycardia	13 (8.6%)	6 (9.2%)	7 (8.1%)		6 (11.1%)	7 (7.2%)	
Bradycardia with poor perfusion	66 (43.7%)	30 (46.2%)	36 (41.9%)		23 (42.6%)	43 (44.3%)	
Pharmacologic measurements							
Epinephrine	139 (92.1%)	61 (93.8%)	78 (90.7%)	0.556[1]	51 (94.4%)	88 (90.7%)	0.539[1]
Number of epinephrine boluses	3.00 [2.00,7.00]	4.00 [2.00,8.00]	2.50 [1.00,4.00]	0.006[2]	5.00 [2.00,9.00]	2.50 [1.00,4.00]	0.002[2]
Highest arterial lactate (0–6 h after)	8.70 [3.90,14.50]	11.96 [4.90,16.26]	5.80 [2.70,12.60]	0.002[2]	11.48 [5.20,16.26]	5.88 [2.85,12.90]	0.002[2]
Lowest arterial pH (0–6 h post-arrest)	7.21 [7.06,7.31]	7.13 [7.02,7.28]	7.27 [7.12,7.34]	0.002[2]	7.12 [7.02,7.25]	7.27 [7.12,7.35]	<.001[2]
EEG CHARACTERISTICS (24 HOURS POST-ROC)							
EEG Background Category				<.001[1]			<.001[1]
Normal	25 (16.6%)	4 (6.2%)	21 (24.4%)		2 (3.7%)	23 (23.7%)	

Table 2 (continued)

		Survival to hospital discharge with favorable outcome			Survival to hospital discharge		
	Overall (N = 151)	No(N = 65)	Yes(N = 86)	P-value	No(N = 54)	Yes(N = 97)	P-value
Slow/Disorganized	98 (64.9%)	34 (52.3%)	64 (74.4%)		29 (53.7%)	69 (71.1%)	
Discontinuous/Burst Suppression	16 (10.6%)	15 (23.1%)	1 (1.2%)		12 (22.2%)	4 (4.1%)	
Attenuated	12 (7.9%)	12 (18.5%)	0 (0.0%)		11 (20.4%)	1 (1.0%)	
Focal abnormalities (n = 148)	42 (27.8%)	24 (36.9%)	18 (20.9%)	0.026[1]	19 (35.2%)	23 (23.7%)	0.127[1]
Periodic / rhythmic patterns (IIC) (n = 145)	7 (4.6%)	3 (4.6%)	4 (4.7%)	1.000[1]	3 (5.6%)	4 (4.1%)	0.697[1]
Variability (n = 120)	79 (52.3%)	18 (27.7%)	61 (70.9%)	<.001[1]	16 (29.6%)	63 (64.9%)	<.001[1]
Reactivity (n = 91)	52 (34.4%)	10 (15.4%)	42 (48.8%)	<.001[1]	7 (13.0%)	45 (46.4%)	<.001[1]
Seizures (n = 150)	8 (5.3%)	7 (10.8%)	1 (1.2%)	0.021[1]	5 (9.3%)	3 (3.1%)	0.131[1]
Spindles (n = 143)	84 (55.6%)	20 (30.8%)	64 (74.4%)	<.001[1]	17 (31.5%)	67 (69.1%)	<.001[1]

ECMO = ExtraCorporeal Membrane Oxygenation. IIC = ictal-inter-ictal continuum.

[1] Fisher's exact test.

[2] Wilcoxon rank-sum test.

Table 3 – Multivariable models of survival with favorable neurologic outcome and survival adjusting for a priori chosen covariates.

	Survival to hospital discharge with favorable outcome (N = 86)		**Survival to hospital discharge (N = 97)**	
	Adjusted Relative Risk(95% CI)	P-value	Adjusted Relative Risk(95% CI)	P-value
EEG Background Category (Numeric)	0.46 (0.35, 0.61)	0<.001	0.53 (0.41, 0.69)	0<.001
Focal abnormalities	0.75 (0.46, 1.22)	0.244	0.72 (0.46, 1.11)	0.138
Spindles	1.92 (1.27, 2.92)	0.002	1.54 (1.09, 2.16)	0.013
Variability	3.31 (1.61, 6.78)	0.001	2.42 (1.31, 4.46)	0.005
Reactivity	3.75 (2.01, 6.99)	0<.001	2.74 (1.61, 4.66)	0<.001

Results are based on multivariable Poisson regression models with robust error estimation.Adjusted for duration of CPR, illness category, age category, PRISM, first documented rhythm, and highest arterial lactate (0–6 h after ROSC).

Table 4 – Stepwise selected multivariable model of survival with favorable outcome adjusting for a priori chosen covariates as well as EEG characteristics.

	Survival to hospital discharge with favorable outcome	
	Adjusted Relative Risk(95% CI)	P-value
PRISM (2–6 h prior to CPR)	0.97 (0.94, 1.01)	0.125
Illness category		0.285
Surgical cardiac	Reference	
Medical cardiac	0.75 (0.49, 1.14)	
Non-cardiac	0.82 (0.57, 1.17)	
Highest arterial lactate (0–6 h after)	0.99 (0.96, 1.02)	0.625
First documented rhythm		0.607
Bradycardia with pulses	Reference	
Asystole	1.04 (0.47, 2.32)	
Pulseless electrical activity (PEA)	1.25 (0.88, 1.79)	
VF/VT	1.24 (0.69, 2.24)	
EEG Background Category (Numeric)	0.46 (0.35, 0.61)	0<.001
Duration of CPR (minutes)		0.707
<6	Reference	
6–15	1.10 (0.74, 1.62)	
16–35	0.85 (0.54, 1.35)	
>35	1.07 (0.67, 1.72)	
Age		0.127
>1 year	Reference	
≤1 year	0.78 (0.57, 1.07)	

Results are based on multivariable stepwise selected Poisson regression models with robust error estimation.

PRISM = Pediatric Risk of Mortality III Score, CPR = cardiopulmonary resuscitation.

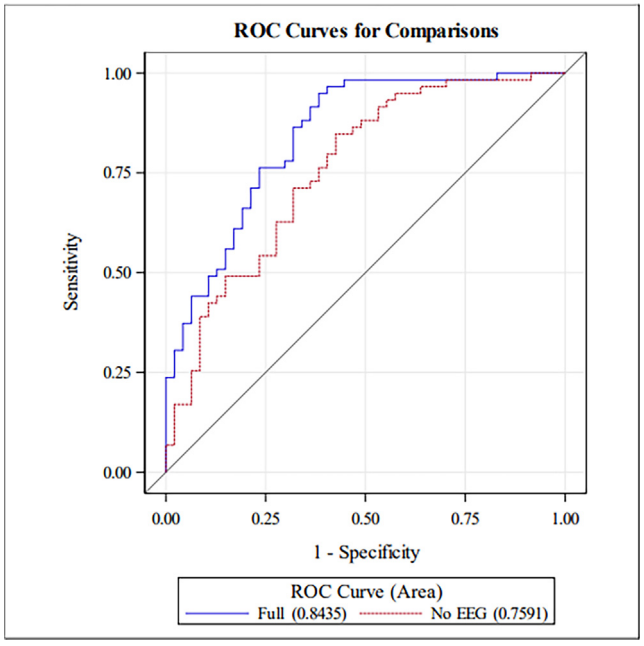

Fig. 2 – Reviver Operator Characteristics (ROC) curve illustrating the area under the curve (AUC) for a prediction model with PRISM score, illness category, highest arterial lactate, CPR duration, first documented rhythm, and age (red line, AUC 0.76), compared to a model with the above variables and the additional of EEG Background Category (blue line, AUC 0.84). The addition of Background EEG Category enhances the accuracy of the model (p = 0.005). Reviver Operator Characteristics Curves for the Prediction of Favorable Outcome. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

retrospective study of 35 children showed that the presence of discontinuous or isoelectric EEG background following an in-hospital or out-of-hospital cardiac arrest was associated with poor neurologic outcome.[48] A larger follow up study demonstrated that a model incorporating EEG Background Category and arrest variables (witnessed status, doses of epinephrine, and initial lactate) predicted unfavorable outcome (AUROC 0.9) and mortality (AUROC 0.83).[11] Another study of both IHCA and out-of-hospital cardiac arrest developed similar prediction models using EEG Background Category in addition to CPR duration and sedation to predict favorable outcomes (AUROC = 0.81).[49] Our results are consistent with these studies that included mixed populations of in-hospital and out-of-hospital cardiac arrests, suggesting that EEG background is a highly valuable biomarker of cerebral injury due to hypoxic ischemic events regardless of arrest location.

Most children with a continuous EEG background (normal or slow/disorganized) survived with favorable outcome. Among this subgroup with milder EEG background changes, likely indicative of less severe brain injury, patients who did not survive with favorable outcome may have had more medical comorbidities given they were more likely to have mild or moderate pre-arrest disability, had higher prevalence of renal disease, and were more likely to be receiving mechanical ventilation prior to CPR. These findings are consistent with prior studies showing that pre-existing renal insufficiency and mechanical ventilatory needs are independent risk factors for mortality following cardiac arrest.[15,16,50,51].

Interestingly, the time to death was later in the cohort with continuous than discontinuous-attenuated EEG Background Category (median 15.7 vs 4.8 days). Patients with more severely abnormal backgrounds may have died during their severe acute illness, more severe post-cardiac arrest syndrome, or because of earlier withdrawal of care, whereas deaths among patients with more normal EEG backgrounds may have resulted from accrued medical comorbidities or secondary adverse events. The potential effects of a self-fulfilling prophecy for an unfavorable neurological outcome based on the clinically available EEG and clinical data cannot be excluded as providers were not blinded to EEG interpretation.[52] Given further clinical details were not collected in the ICU-RESUS trial, we could not determine how these factors interact. Future and ongoing studies, including the Pediatric Influence of Cooling duration on Efficacy in Cardiac Arrest Patients (p-ICECAP; NCT05376267) study which attempts to limit the influence of early EEG and neurological exams on decisions for early withdrawal of life sustaining therapies, may provide unique insight into the impact of a self-fulfilling prognostic prophecy.[53]

These data are not generalizable to all pediatric IHCA patients. Importantly, this study excluded children with a baseline of severe functional disabilities (PCPC 4 and 5) since patients with neurological dysfunction at baseline might have an abnormal EEG prior to a cardiac arrest, and abnormalities on the post-arrest EEG would be difficult to attribute to new neurologic injury. Additionally, we excluded patients < 90 days old to enable more accurate characterization of EEG features which vary by age.[25] Healthy infants have discontinuous EEGs during sleep and lack sleep spindles until two–three months of age. Both features are associated with post-arrest outcomes. Of note, the one patient with an attenuated background who survived with favorable neurologic outcome was a premature infant whose corrected gestational age was < 90 days. This highlights the need to interpret EEG findings in the context of corrected gestational age as the expected patterns in response to injury changes with age.[54] Finally, only 24% of the patients from the parent study underwent EEG monitoring within 24 h of IHCA and thus were eligible for this study. This may be due to institutional variability in EEG monitoring practice, and this study may include more patients from institutions with more resources and standardized post-arrest guidelines. Additionally, children who return to their neurologic baseline after cardiac arrest may not undergo EEG monitoring such that children included in this study may have had more severe early post arrest neurologic injury.

Our study has several limitations. First, the study lacks long-term neurobehavioral outcomes, focusing only on the PCPC score at hospital discharge. Second, we assessed EEG features present in the first 24 h post-ROC and did not account for more subtle changes over time, or in comparison to a patient's pre-arrest EEG. Prior studies have shown that a rapidly improving EEG portends a better prognosis.[55] Third, the use of EEG reports rather than standardized re-review of the EEG tracings limited analysis to features described in the clinical EEG report and known to have high interrater reliability in clinical practice [56] Fourth, we could not account for the effect of sedating medications or patient's body temperature on the EEG background as this data was not collected in the parent study. Fifth, the presence of seizures or status epilepticus was not evaluated as part of our predictive model since few patients experienced seizures.

Prior studies have demonstrated status epilepticus is a risk factor for worse neurologic outcomes.[11,57–59] Finally, we did not collect mode of patient death and cannot account for the effect a very abnormal EEG background had on decisions surrounding withdrawal of care.

In summary, in this secondary analysis of the ICU RESUS trial, EEG Background Category in the first 24 h following IHCA in children with normal to moderate disability at baseline was the variable most predictive of survival with favorable outcome and survival to discharge. The addition of EEG Background Category to clinical variables improved predictive accuracy for outcome.

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CRediT authorship contribution statement

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A (continued)

First	M	Last	Degree	Department	Institute	City	State	County
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Appendix B. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.resuscitation.2024.110271.

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