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An Enhanced Cerebral Recovery Index For Coma Prognostication Following Cardiac Arrest

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Abstract

Prognostication of coma outcomes following cardiac arrest is both qualitative and poorly understood in current practice. Existing quantitative metrics are powerful, but lack rigorous approaches to classification. This is due, in part, to a lack of available data on the population of interest. In this paper we describe a novel retrospective data set of 167 cardiac arrest patients (spanning three institutions) who received electroencephalography (EEG) monitoring. We utilized a subset of the collected data to generate features that measured the connectivity, complexity and category of EEG activity. A subset of these features was included in a logistic regression model to estimate a dichotomized cerebral performance category score at discharge. We compared the predictive performance of our method against an established EEG-based alternative, the Cerebral Recovery Index (CRI) [1] and show that our approach more reliably classifies patient outcomes, with an average increase in AUC of 0.27.

I. Introduction

Every year there are approximately 800,000 sudden cardiac arrests in the United States and Europe with survival rates of approximately 10% [2,3]. Of those that survive, 80% enter a comatose state after resuscitation and only 3–7% regain normal neurological status [2,4]. The ability to accurately assess the extent of anoxic damage, and neurological outcome is of immense concern to families, hospitals and care providers alike. In addition to the obvious emotional cost of care for families, the financial burden can be steep, running up to $20,000 a day, with stays lasting from hours to weeks.

Despite the existence of several animal-based models in the literature [4-7], a neurological examination by a physician remains the method of choice for gauging neurological outcomes. These qualitative evaluations can be problematic, however, as they require doctors to grapple with a complex interacting array of confounding factors including anesthesia, cooling protocols and patient age, all of which influence the characteristics of the multichannel EEG data streams. There exist industrial solutions (which aim to measure

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depth of anesthesia) that have been adapted for use in comatose outcome prediction with some success [8]. Unfortunately, these methods are most often proprietary, which prohibits critical evaluation and continuous improvement in a domain where the cost of misclassification is tremendous. One open source quantitative method that has been used with some success is the Cerebral Recovery Index (*CRI*) [1]. Developed in 2013, the CRI is an important example of a publically available algorithm that can run at the bedside for outcome prognostication. Despite its demonstrated potential, the CRI makes several heuristic assumptions, and might benefit from a more principled approach. In this paper, we present an enhanced CRI (eCRI), which we believe will provide greater robustness and utility at the bedside for outcome prognostication.

One of the central reasons that effective predictive models of comatose outcomes are difficult to realize is a lack of available physiologic and clinical data documenting the evolution of brain activity features following cardiac arrest, through to the outcome of interest. Accordingly, in addition to the eCRI, we introduce a novel multi-institutional database, which we collected to facilitate this study.

II. Literature Review

One prospective study by Oddo et al. compared the performance of smoatosensory-evoked potentials, serum neuron-specific enolase, EEG, and clinical exams in an attempt to identify the features that were most efficacious for the postanoxic coma prognostication problem utilizing a cohort of 134 patients treated with therapeutic hypothermia [13]. They identified EEG reactivity, incomplete brainstem reflexes after re-warming, and neuron-specific enolase as strong independent predictors of outcome at 48 hours following the arrest. The prediction of outcome was performed using ordinal logistic regression, and the combinations of features were found to have an AUC of 0.89.

Another study by Stammet et al. investigated the efficacy of multimodal prognostication in 75 post-cardiac arrest patients treated with hypothermia post-resuscitation [3]. Neuronal health was measured 48 hours after arrest using neuron-enriched s100β and neuron-specific enolase (NSE). The Bispectral index of the patients (an indicator of the depth of anesthesia) was also continuously measured over the first 48 hours following the arrest. Utilizing a logistic regression model, Stammet et al. found that a combined NSE, s100β and BIS measures had significant predictive value, with AUC=0.95 at 48 hours following the arrest.

It is clear from the literature that a combination of EEG features, NSE measures, and brain stem function after re-warming can reliably predict patient outcomes within 48 hours after resuscitation. The CRI, however, provides evidence that an equally reliable prediction might be made much sooner. It follows that our goal in this study is not simply to predict patient outcomes, but to do so as quickly and reliably as possible.

III. Methods

A. Data

We collected retrospective data from 52 patients at the Massachusetts General Hospital (MGH), 89 patients from the Brigham Women's hospital (BWH) and 26 patients from the University Hospital of Lausanne (UHL), Switzerland. All data were collected under protocols approved by the local Institutional Review Board and de-identified to protect patient privacy. EEGs were collected using the standard 10-20 montage. Table 1 provides summary statistics of the population-level features for the collected sample. The cardiac rhythms at arrest for the sample were 16.16% Asystole, 35.92% Pulseless Electrical Activity (PEA) and 44.31% Ventricular Fibrillation (VF) with 3.61% having unknown rhythms at arrest. In the final column of Table 1 we provide Spearman correlation coefficients of each feature with the Cerebral Performance Category (CPC) of the sample at hospital discharge. All patient data were epoched into 5-minute intervals for feature extraction and later analysis.

B. Features, Outcome and Validation

The selected population-based features investigated are shown in Table 1. We also extracted EEG-based features, from each available channel. We sought features that would quantify the complexity, connectivity and category of the recorded EEG. Many of these features have a history of use in EEG analysis more generally while others were designed for their potential relevance to cardiac arrest prognostication specifically [1]. Our complexity features included Shannon's Entropy (*Hsh*), Tsalis Entorpy (with q=2, $Ht_{q=2}$) [5], the average signal coherence in the delta band across channels (COH_{δ}) and Cepstrum coefficients ($CP_{1:2}$) [11]. The maximum Phase Lag Index across channels was used as a measure of connectivity (PLI_{max} [12], while standard deviation (*SD*), a measure of burst to a measure of burst suppression called signal regularity (*REG*) [1], EEG alpha to delta band power ratio (*ADR*), and a binary low voltage state measure (EEG less than 5 microVolts, $LV_{5\mu}$) characterized the EEG category.

Our outcome of interest was the Cerebral Performance Category (*CPC*) of the patients at discharge [10]. *CPC* is a score provided by clinicians to describe the range of neurological outcomes upon discharge with 5 indicating brain death, and 1 indicating minimal neurological insult.

We denote our feature data for each patient as $X_i \in \mathbb{R}^{c \times f \times e^i}$. Where $i \in 1{:}\ N$ and i denotes the patient number, e^i denotes the number of 5 minute epochs for a given patient, c denotes the number of EEG channels, f denotes the number of features and N denotes the number of subjects. Given data of this form, we are interested in building a model that will allow us to predict positive and negative neurological outcomes defined as:

$$Y_i = \begin{cases} 1, & CPC \leq 2 \\ 0, & CPC > 2 \end{cases}$$

In our case, the small sample size (N) necessarily calls into question the potential extensibility of any model we choose to develop. To account for this issue, we employed leave one out cross validation (LOOCV), which repeatedly breaks the data into model training sets $\{X_j, Y_j \forall j \neq i\}$, and testing sets $\{X_i\ Y_i\}$ for each individual in our population, mirroring the real-world scenario of testing the system only on cases not previously used to train the model.

C. EEG Pre-processing and Artifact Detection

Subjects had varying lengths, densities and sampling rates of recorded EEG data. To address these discrepancies, we bandpass filtered the data between 1 and 50 Hz, re-referenced the data to zero-mean to account for any DC offset in the EEG, and downsampled the signal to 100Hz.

EEG data are prone to a wide range of artifacts that can infringe upon the quality and accuracy of quantitative estimates. To address these issues we employed a multifaceted artifact detection strategy. First, we identified any 5-second EEG segments that were deemed to be statistical outliers. That is, segments which were 3 or more standard deviations from the overall population's variance, kurtosis, or skew. Second, we identified artifacts with known spectral signatures including muscle and eye components. Lastly, we identified spikes (defined as segments >1 mV), and channel disconnections (defined as segments where Voltage = 0). After artifact detection, each subject was assigned a weight vector $w_i \in \mathbb{R}^{c \times e^i}$, describing the proportion of data in each epoch, on each channel, which was affected by artifact.

D. Modeling Approach

The standard CRI is formally defined as:

$$CRI = \frac{\widehat{SD}}{4}\left(\widehat{ADR} + \widehat{Hsh} + \widehat{COH}_\delta + \widehat{REG}\right) \quad (1)$$

where $CRI \in [0,1]$ and a higher CRI denotes a higher probability of a positive outcome. The CRI utilizes normalized versions of several features already described: $\widehat{SD}$, $\widehat{Hsh}$, $\widehat{COH}_\delta$, $\widehat{REG}$ and $\widehat{ADR}$. These features are normalized using a sigmoidal transform whose coefficients were selected heuristically by the investigators.

Importantly, the CRI is a non-spatial, time-independent indicator of comatose outcome following cardiac arrest. That is, EEG activity measured at differing channels and times are modeled as equally predictive of outcome class.

Our enhanced CRI (eCRI) exhibits the same assumptions, and was therefore generated by collapsing the data in our training set across epochs, and using the median channel value to designate a feature set $P_{X_i} \in \mathbb{R}^{f \times \Sigma_{j \neq i} e^i}$, and corresponding outcome vector $P_{Y_i} \in \mathbb{R}^{1 \times \Sigma_{j \neq i} e^i}$ for each patient. Next, we specified a model with a similar form as the CRI, but with coefficients that were determined in a formal statistical way. A simple and intuitive model to

accomplish this goal is a logistic regression, which, like the CRI, provides a mapping between continuous features and a binary outcome. The enhanced CRI is computed as:

$$eCRI = \frac{1}{1+e^{-\left(\beta_0 + X_i^T \beta\right)}} \quad (2)$$

where $\beta_{0:x}$ describe the model coefficients. Given the large number of features and small sample size, we utilized stepwise regression to select features that improved the model's Bayesian Information Criteria (BIC). BIC is a useful criteria in cases like ours as it penalizes features with a low contribution to the model's overall performance. Additionally, we weighted data residuals by the weights w_i, (derived in our artifact detection phase) during parameter optimization. This allowed us to explicitly account for noisy data epochs as less reliable, without removing them from consideration entirely.

IV. Results

We computed the CRI and eCRI on the subset of our data from the MGH. The weighted stepwise regression identified the following features as important predictors of comatose outcome: $Ht_{q=2}$, REG, COH_{δ}, CP_2, $LV_{5\mu}$, PL_{max}, age, and ROSC. The parameter estimates, and their statistical significance are illustrated Table 2. Importantly, all features were found to have a statistically significant relationship with the CPC at discharge ($p < 0.05$). The results in Table 2 indicate that an increase in entropy, age, regularity, coherence in the delta band, ROSC, phase lag index, age or a low voltage EEG diminish the probability of positive neurological outcome. The results also indicate that an increase in signal Cepstrum (a measure of the rate of change in the spectrum) improves the probability of a positive outcome.

In Figures 1 and 2 we illustrate the standard and enhanced CRI indices applied to the patient sample respectively. Figure 1 demonstrates that the standard CRI measure is able to distinguish between the two groups effectively within approximately 24 hours of EEG initiation. Unfortunately, the estimate is incongruous with the purpose of the measure itself. That is, the score was designed to provide higher values for patients with strong probabilities of recovery, which is not what we observed. Figure 2 shows the results of our enhanced index on the same patient sample.

Importantly, the eCRI effectively distinguishes between the two groups from the onset of EEG recording and, on average, does a better job distinguishing between the two patient classes. The timeliness of our approach is especially worth highlighting, as care for comatose patients is costly, both emotionally and financially.

To quantify more precisely the abilities of the models to distinguish between the two patient groups, we computed the AUC at each hour following EEG initiation using LOOCV. We also compared the performance of our method against the CRI's compliment (1-CRI) to ensure a fair comparison of overall classification abilities of the two approaches.

The results of our analysis are shown in Figure 3. Comparing the AUC of our approach to the CRI, there is a clear improvement in the classification performance, with a mean AUC

improvement of 0.26. In comparing our model against the CRI's complement we observe that our approach more robustly classifies outcomes in the first 24 hours, while the traditional CRI is better able to classify outcomes after 24 hours. Temporal differences in performance aside, our model exhibits an overall classification improvement of 0.075 above the CRI's complement.

V. Conclusion

In this study, we looked for global, time-independent indicators of comatose outcome following cardiac arrest. We developed an alternative model to an existing quantitative estimate of neurological outcome, the CRI, using a dataset of patients from the Massachusetts General Hospital. We demonstrated an improvement in the overall classification performance of our model, as compared to the CRI.

We view our results as an encouraging first step towards the development of more rigorous quantitative estimates for the prognostication of coma outcomes in critical care settings and anticipate enhanced results with additional data, and the deployment of more rigorous techniques that account for time explicitly. Importantly, this work also described techniques that will facilitate and accelerate the collection of more data in this area, and thereby allow for the development of larger datasets, with greater statistical power, and enhanced predictive performance.

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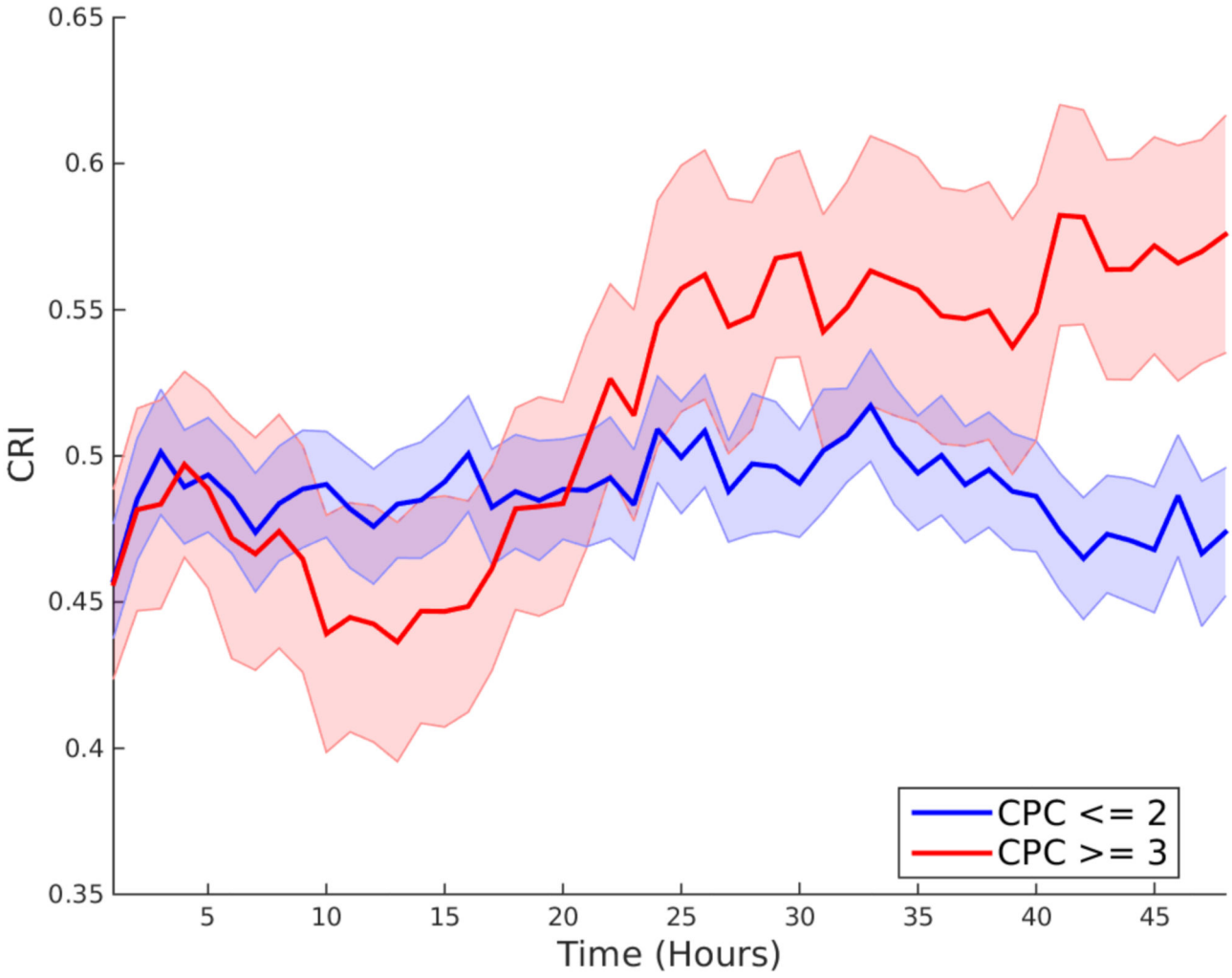

Figure 1.
The original CRI. The blue line signifies patients with positive neurological outcomes (CPC <=2), and the red line signifies patients with negative neurological outcomes (CPC >=3). Shaded areas represent the standard error of the sample.

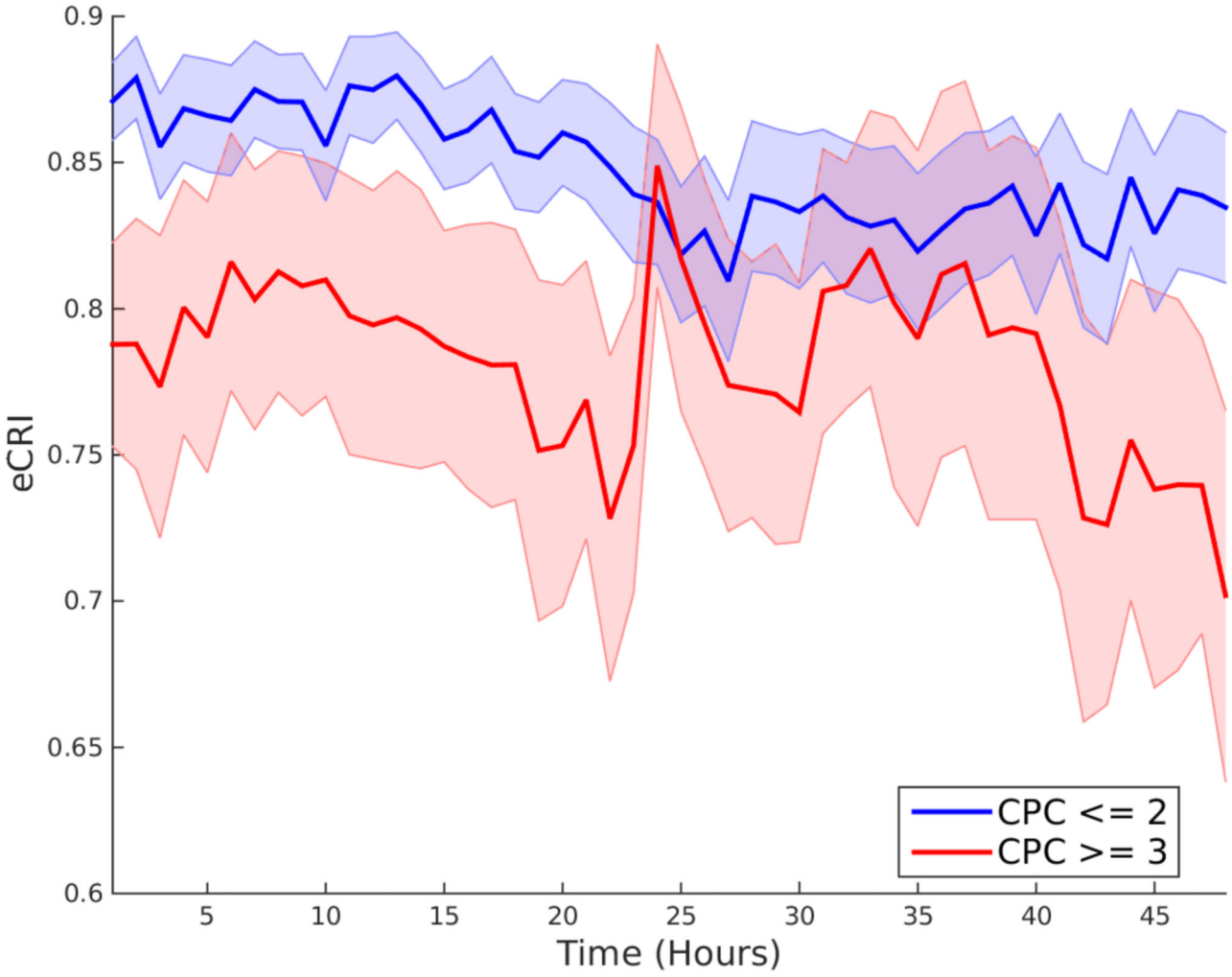

Figure 2.

Our enhanced CRI. The blue line signifies patient with positive neurological outcomes (CPC <=2), and the red line signifies patients with negative neurological outcomes (CPC >=3). Shaded areas represent standard error of the sample.

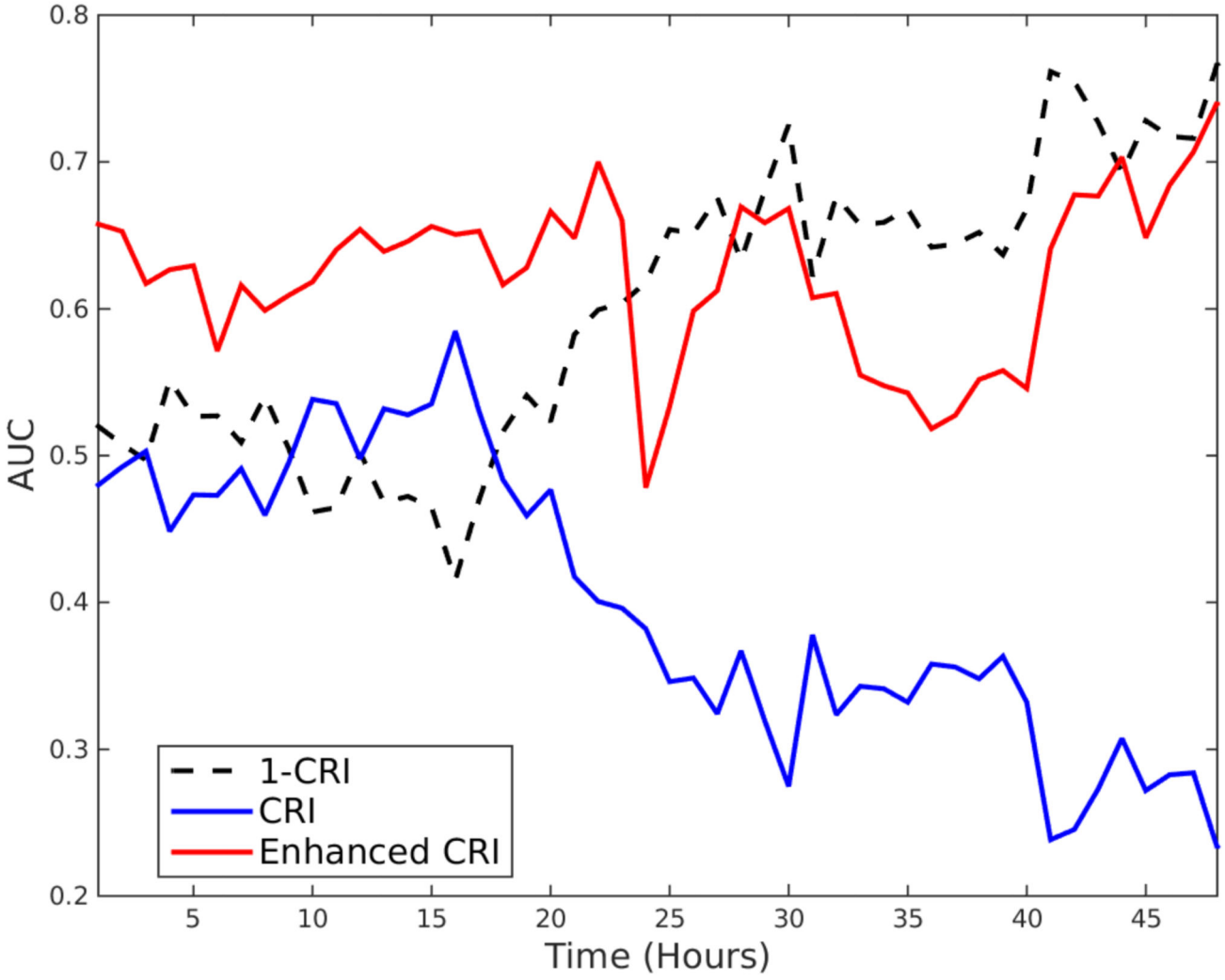

Figure 3.
Comparison of overall classification performance overtime for the CRI, eCRI, and CRI's compliment.

Table 1

Summary statistics for our patient sample.

	Mean	SD	CPC (corr/pval)
Age	59.59	17.23	0.23 / <0.05
Gender (% male)	58	-	0.04 / >0.05
ROSC (min)	26.53	23.25	−0.13 / <0.05
Weight (kg)	88.31	21.58	−0.08 / >0.05
Therapeutic Hypothermia (%)	86	-	0.22 / >0.05
OHCA (%)	82	-	0.19 / >0.05
CPC at discharge	3.67	1.70	-
CPC at 3 months	4.04	1.65	-
CPC at 6 months	3.81	1.81	-

Abbreviations: time until return of spontaneous circulation (ROSC); standard deviation (SD); out of hospital cardiac arrest (OHCA); cerebral performance category (CPC).

Table 2

Parameter values and statistical significance for the eCRI logistic regression with artifact-weighted residuals.

	Parameter Estimate	t-stat	p-value
Intercept	−6.57	−6.24	<0.01
$Ht_{q=2}$	1.71	2.15	0.03
REG	2.91	6.86	<0.01
COH_{δ}	2.23	6.44	<0.01
CP_2	−1.13	−5.46	<0.01
$LV_{5\mu}$	5.06	13.99	<0.01
PL_{max}	1.68	4.89	<0.01
Age	0.03	9.55	<0.01
ROSC	0.02	5.91	<0.01