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Quantitative EEG trends predict recovery in hypoxic-ischemic encephalopathy

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AUTHOR CONTRIBUTIONS

M.M.G., E.A., J.W.L., E.N.B., S.S.C., R.M., M.B.W. contributed to conception and design of the study. M.M.G., E.A., and M.B.W. contributed to analysis of data. M.M.G., E.A., M.B.W. contributed to preparing the figures. M.M.G., E.A., T.A., J.W.L., S.H., A.S., N.G., S.B., V.M.J., M.B.W. contributed to data acquisition. M.M.G., E.A., T.A., J.W.L., E.N.B., S.S.C., R.M., M.B.W. S.H., A.S., N.G., S.B., V.M.J., E.N.B., S.S.C., R.M. contributed to drafting the text.

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POTENTIAL CONFLICTS OF INTEREST

Nothing to report.

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Abstract

Objective: Electroencephalogram (EEG) features predict neurological recovery following cardiac arrest. Recent work has shown that prognostic implications of some key EEG features change over time. We explore whether time dependence exists for an expanded selection of quantitative EEG (QEEG) features and whether accounting for this time-dependence enables better prognostic predictions.

Design: Retrospective.

Setting: Intensive care units at four academic medical centers in the U.S.

Patients: Comatose patients with acute hypoxic-ischemic encephalopathy.

Interventions: None.

Measurements: We analyzed 12,397 hours of EEG from 438 subjects. From the EEG, we extracted 52 features that quantify signal complexity, category, and connectivity. We modeled associations between dichotomized neurological outcome (good vs. poor) and QEEG features in 12-hour intervals using sequential logistic regression with Elastic-Net regularization. We compared a predictive model utilizing time-varying features to a model using time-invariant features and to models based on two prior published approaches. Models were evaluated for their ability to predict binary outcomes using area under the receiver operator curve (AUC), model calibration (how closely the predicted probability of good outcomes matches the observed proportion of good outcomes), and sensitivity at several common specificity thresholds of interest.

Main Results: A model utilizing time-dependent features outperformed (AUC = 0.83 ± 0.08) one trained with time-invariant features (0.79 ± 0.07, $p<0.05$) and a random forest approach (0.74 ± 0.13, $p<0.05$). The time-sensitive model was also the best-calibrated.

Conclusion: The statistical association between QEEG features and neurological outcome changed over time, and accounting for these changes improved prognostication performance.

Keywords

EEG; quantitative EEG; hypoxic-ischemic encephalopathy; cardiac arrest; machine learning

INTRODUCTION

Over 500,000 cardiac arrests occur every year in the United States.(1) Most patients sustain severe brain injury resulting in coma.(2) Despite recommendations to postpone prognostication at least 72 hours post-arrest, the most common proximal cause of mortality is early withdrawal of life-sustaining therapies.(3, 4) There is a need for accurate methods to assign probability of good and poor neurologic outcome early after cardiac arrest, to reduce subjectivity, and avoid poor outcomes as a result of self-fulfilling prophecies.

Specific electroencephalogram (EEG) patterns are associated with eventual recovery from coma due to hypoxic-ischemic encephalopathy (HIE) after cardiac arrest.(5, 6) However,

existing EEG review practices rely on visual analysis, which does not translate into reproducible quantitative predictions of neurologic outcome.(7–15) Several studies have shown that several quantitative EEG (QEEG) features may carry prognostic information that is useful in outcome prediction on HIE.(6, 13, 16–25) More recent models have achieved promising results by combining several QEEG features (26) and leveraging local temporal trends of multiple QEEG features.(5)

In this study, we hypothesize that a machine-learning method can predict long-term neurologic outcome in HIE by integrating clinical data to existing and novel QEEG features. Our work goes beyond prior results by using a more comprehensive set of QEEG features, more completely leveraging temporal trends, and by rigorously characterizing statistical performance of the model.

MATERIAL AND METHODS

Subjects and clinical management

Adult subjects diagnosed with in- or out-of-hospital cardiac arrest from October 2009 to April 2016 in four university-affiliated hospitals in the U.S (Massachusetts General Hospital; Brigham and Women's Hospital; Yale New Haven Hospital; and Beth Israel Deaconess Medical Center) were retrospectively reviewed. Subjects who were comatose after return of spontaneous circulation (ROSC) underwent continuous EEG monitoring and received targeted temperature management (TTM) with goal temperature of 32–34°C were screened (TTM 36°C was not used at the time of data abstraction). Retrospective data collection and analysis was performed under independent Institutional Review Board approvals at participating hospitals and informed consent was waived.

Data collection and functional outcome assessment

Clinical and outcome information were collected retrospectively. Subjects were stratified by age, gender, time to ROSC, and initial cardiac rhythm, dichotomized as shockable (ventricular fibrillation or ventricular tachycardia) or non-shockable (asystole, pulseless electrical activity, and unknown).

The primary outcome was defined as the *best* neurological function achieved up to 6-months after initial cardiac arrest, according to the Glasgow-Pittsburgh Cerebral Performance categories (CPC) scale, ascertained by medical record review (E.A., M.M.G, J.W.L., S.H., S.A., and M.B.W.). "Good" outcome was defined as a CPC score of 1 or 2 and "poor" functional outcome as a CPC of 3 to 5.(28) All patients had CPCs assessed at discharge. Patients with CPC 3 and 4 were further assessed by chart review to determine whether they achieved a better CPC (1 or 2) in the following 6 months. CPC was chosen both because it is widely used in neurologic outcomes studies, and is simple enough to be easily ascertained via chart review. Prior studies have shown that CPC can be extracted reliably via chart review.(27) Reliability is further enhanced in our study by the lumping together of CPC scores into dichotomous "good" and "poor" outcomes.

EEG data acquisition

Continuous EEG monitoring was started at each institution as early as possible during TTM and maintained for 24–72 hours, unless the subject regained consciousness, had life-sustaining therapies withdrawn, or died. Digital EEG was recorded using the international 10–20 system. EEG was analyzed up to 72 hours of monitoring. EEG preprocessing and artifact detection were performed prior to feature acquisition (Supplementary materials). §

QEEG features extraction

We extracted 52 QEEG features: 45 single-channel and 7 multi-channel (see Supplementary Materials; Table s1).(26, 29–39) Single channel features were computed on the following frontotemporal electrodes: Fp1, Fp2, F3, F4, F7, F8, and Fz. Multi-channel features were computed on the 21 unique pairs of the selected frontotemporal electrodes. To reduce feature dimensionality, the mean value of the extracted features across all channels was used. All EEG features were z-scored (i.e. scaled to zero mean and unit variance). A more detailed description of the QEEG features extracted, corresponding equations, and QEEG processing pipeline is available in the supplementary materials and online repository (Supplementary materials, Table s1). §

The 52 QEEG features fell into three EEG signal property domains: a) Complexity features (21 total) quantify the degree of randomness or irregularity in the EEG signal (29, 30, 35–39); b) Category features (24 total) quantify the degree to which brain states fall into certain key EEG patterns likely to carry prognostic significance (26); c) Connectivity features (7 total) quantify interactions across electrodes.(26, 31–34) All analyses were performed using MATLAB 2016a (Natick, MA, USA).

Statistical analysis

Univariate Analysis—We began our study exploring Spearman correlations between our 56 features (52 QEEG and four clinical) and CPC scores at consecutive 12-hour time blocks, up to 72 hours.

Sequential Logistic Regression with Elastic Net Regularization—The prognostic importance of EEG features changes over time.(5, 26) We accounted for this evolution in the feature-outcome relationship by training a *contiguous sequence of logistic regression models*, one for every 12 hours of EEG. All subjects with EEG discontinued *before* the end of a given time interval (e.g. before 48h in the 36–48h interval) were excluded for the model trained *within* that interval. Therefore, each model was trained to predict 6-month neurologic outcome for subjects still monitored to the end of a given interval. Each model in the sequence included feature information from the current time interval, *and* feature information from preceding time intervals (e.g. the model at 36 hours contains feature information from hours 1–12, 13–24, and 25–36). This approach allowed models later in the sequence to consider both past and present feature information when making predictions. The number of subjects available for modeling purposes in each of the 12-hour time

§To aid in reproducibility of this study, we have made our feature extraction code public: https://github.com/deskool/ComaPrognosticanUsingEEG

intervals, and their outcomes, are displayed in Table 1. In Figure 1, we graphically illustrate our approach. Features are selected using an Elastic Net model (see Supplementary Materials)(40). Henceforth, we refer to the Elastic Net regularized sequential logistic regression model as the *time-sensitive* model.

Baseline Models—We compared the time-sensitive model to four baseline approaches: (1) A clinical baseline: a logistic regression using age, gender, ROSC and initial rhythm; (2) a time-insensitive model: a logistic regression model using features selected by Elastic Net *across all time intervals, but retrained within each time-interval*; (3) the 2013 Cerebral Recovery Index (CRI): a heuristic approach using alpha/delta band-power, standard deviation, coherence in delta band, Shannon entropy, and regularity; (4) a Random Forest: a Random forest classifier with features and settings inspired by the 2017 CRI. (5) The CRI methods were selected as literature baselines given their impressive reported performance. The 2017 CRI used the five features from the 2013 study, in addition to four features that characterized burst-suppression activity. The authors reported these additional features provided modest improvements in model performance compared to a Random Forest classifier using the original five features. For this reason, we used the five CRI features from the 2013 model when implementing the Random Forest classifier.

Performance Characterization Metrics—We evaluated model performance using EEG data for each consecutive 12-hour interval, up to 72 hours. Performance metrics included *Area Under the Receiver Operator Curve (AUC)*, used to evaluate the model's ability to make binary predictions, and the sensitivity and specificity for specific operating points on the ROC curve; and *statistical calibration*, which measures how well the observed proportions of good outcomes match predicted probabilities. Calibration is particularly important for our model when used as a risk-score.

Model Validation Approach—All models were validated using 10-fold cross validation. That is, we partitioned available data into ten folds. In each fold, 90% of the data was used to identify model parameters and the remaining 10% were used to evaluate model performance on subjects never seen in the corresponding training sets. Subjects within each testing fold were unique. We used the average performance of models across the unseen testing sets in the ten folds when comparing performance. Feature selection was performed using an Elastic Net with 10 *inner validation folds* (supplementary materials).

RESULTS

Data Characteristics

We identified five-hundred and thirty-six subjects across the four contributing hospitals. Seventy-six subjects were excluded from final analysis due to missing admission clinical information and 22 were excluded due to insufficient EEG recording quality or missing outcome assessments. The 438 remaining subjects had 12,397 hours of EEG data available.

By hospital discharge, 120 subjects had CPC of 1–2 and 281 subjects had a CPC of 5 (401/438, 91.6% of subjects). The remaining 8.4% (37/438) had a CPC of 3 or 4 at discharge. Among these, 14 ultimately improved to a CPC score by 6-months of 1 or 2, five

remained with CPC of 3–4, and 10 died. For the remaining 8 cases (1.8% of 438), 6-month outcomes could not be determined by chart review. For these the discharge CPC score was carried forward and taken as the final outcome. In Table 1, Table s1 and Table s2, we summarize subject characteristics.

Univariate Analysis

Table s3 displays univariate Spearman correlations between features, and the CPC scores in contiguous 12-hour intervals. Several QEEG features were predictive exclusively in specific time windows (time-sensitive), with correlation weights varying over time. Figure s1 illustrates three examples of features whose relationship with the most probable outcome changes over time, and three features whose prognostic value over time is stable.

Performance Characterization

We evaluate the ability of the models in two ways: First, to make *accurate binary predictions* (good vs. poor outcome), and second, to function as a *risk scoring system* by predicting the probability of a good (or, complementarily, a bad) outcome.

Performance in predicting binary outcomes: in Figure 2 we compare the time-dependent AUC of the time-sensitive model to baseline approaches. Note that, the model for each time point is trained only EEG data from subjects who survived and remained on EEG up to that time; model predictions likewise pertain only to those who remain on monitoring. Here the time-sensitive approach performed best, exhibiting consistent improvements in performance ($p < 0.04$, according to 2-sample t-test) with increased observation time (from AUC of 0.71 ± 0.05 at 12 hours to 0.79 ± 0.08 at 72 hours). The leave-one-institution-out cross-validation results are available in the supplementary materials (Figure s2).

With regard to *overall area under the receiver operating curve,* AUC_0 (Figure 2 and Table s4), the time-sensitive model accurately predicted 6-month functional outcome ($AUC_0 = 0.83 \pm 0.08$ across the 10 testing folds) compared to the time-insensitive model ($AUC_0 = 0.79 \pm 0.07$), Random Forest ($AUC_0 = 0.74 \pm 0.13$), original CRI ($AUC_0 = 0.69 \pm 0.07$), and clinical baseline model ($AUC_0 = 0.68 \pm 0.05$). The improvement in prediction performance was statistically significant according to a 2-sample t-test ($p < 0.05$). In Figures 3 we report the overall sensitivity and specificity of the time-sensitive model over time. Table s5 and Table s6 contain sensitivity and specificity data for time-sensitive and time-insensitive models.

Final Model Using All Data

Table s7 shows coefficients for features selected by the time-sensitive model trained using *all available data*. The association of QEEG features with functional outcome varied across time. Not all types of EEG complexity positively correlated with outcomes. Fractal Dimension and False Nearest Neighbor were associated with poor outcomes while Entropy and Cepstrum coefficients were associated with good outcomes. As expected, the association between outcome and EEG category depended on the particular category: epileptiform activity was associated with poor outcomes while regularity (a measure of continuity) was

associated with good outcomes. Increased connectivity between channels was consistently associated with poor outcomes.

Certain features were more predictive early on (Tsallis entropy, autoregressive-moving average, and coherence in the delta band) while other features were more predictive later (number of sharp waves, fractal dimension, and cross correlation magnitude).

DISCUSSION

The technical contribution of this study lies in the methodological approach we developed. Our modeling framework reflects the decision process of care providers, considering information across multiple points in time when predicting outcomes. We showed that the QEEG model which retains “memories” of previously encountered features outperformed state-of-the-art approaches which used only present features. The time-sensitive model had the best classification (overall $AUC_0 = 0.83 \pm 0.08$) and statistical calibration of all tested approaches (Figure 4 and Table s5). These test characteristics show that our model makes well-calibrated predictions. That is, the observed proportions of good outcomes match the predicted probabilities of good outcomes quite well. The superior calibration of our time-sensitive model provides strong motivation for its use as a risk score. In Figure s3, we illustrate how outcome probabilities of the model could be used to score patient risk in a continuously updated fashion. An important strength of this study was its multicenter nature, incorporating data from four institutions and more than 400 subjects.

Several features selected by our final model reflect prior findings in the literature. We found that information theoretic measures of EEG complexity and regularity were predictive of good functional outcomes while features measuring epileptiform discharges were associated with poor outcomes.(5, 17, 19, 22, 26, 41, 42) Two EEG complexity features (Cepstrum and Tsallis entropy) and EEG regularity contributed to predictions in the first 24 hours of monitoring. These findings substantiate prior reports that specific EEG signatures observed during the first 24 hours after cardiac arrest have strong predictive value despite hypothermia and sedative use.(15) Other QEEG features available to our model, but not selected, have been previously reported as useful in HIE prognostication. These include measures of spectral content and burst-suppression.(5, 13, 16–18, 20, 22–26, 41) This apparent difference from previous literature is likely due to our feature selection method, which when faced with multiple informative but correlated features chooses among them. Thus, features that have significant predictive value individually are not necessarily retained in the final multivariate prognostication model.

Our model demonstrates that EEG provides valuable prognostic information early after cardiac arrest, and that temporal trends can be used to further improve predictions. The time-sensitive model performance continued to improve as more data became available, highlighting the incremental prognostic value of continuous EEG beyond 24 hours.(5, 15, 18, 19)

In our analysis, the time-sensitive method outperformed a Random Forest classifier and the original CRI model utilizing five QEEG features.(5, 26) We note that the performance of our

Random Forest implementation was inferior to that reported by Tjepkema-Cloostermans et al. (AUC = 0.90 at 24 hours).(5) The discrepancy may result from: (1) the heterogeneity of our data, which came from four different centers compared to the authors' two-center study, (2) our decision to align data with respect to the start of EEG recording rather than the time of cardiac arrest, and (3) use of more extensive validation (10-fold versus 1-fold).

Limitations

This study has several limitations. We have attempted to address each of them at least in part, but further work remains.

1) Our method focused on EEG and initial clinical features. A multi-modal prognostication strategy integrating data from serial neurological exams, notably the pupillary reflex and Glasgow Coma Score, somatosensory evoked potentials, neuroimaging, serum biomarkers, visual EEG review could likely provide further improve prognostic predictions. Future studies need to investigate whether QEEG analysis improves on current multimodal prognostication methods.

2) Outcome data beyond hospital discharge was missing for some subjects with CPC 3 or 4 at discharge; however, this problem was limited to 1.8% (8/438) of subjects. A sensitivity analysis excluding these cases showed no significant change in prediction performance, therefore we do not believe that loss to follow up in this small subpopulation significantly affected our results.

3) The duration of EEG monitoring was not uniform across all subjects. This is typical of retrospective studies in this population and is reflected in the decline in prediction calibration after 48 hours. For pragmatic reasons (to facilitate training machine learning models), we aligned EEG data based on time of initiation of EEG rather than time of ROSC. This caveat may decrease interpretability of our findings regarding how QEEG features change across time from initial injury. However, this data alignment facilitated deployment of a sequential model that requires feeding features forward from one-time interval to another, which would be compromised if large sections of data from the first 12 hours were unavailable. A visual representation of the time to ROSC compared to the time of EEG initiation in Figure s4.

4) Healthcare providers participating in decision making regarding life-support were not blinded to EEG results, therefore we cannot exclude that self-fulfilling prophecies affected the outcomes observed and which features were most predictive in our QEEG model.

5) Some drugs administered to cardiac arrest patients are known to modulate the EEG (e.g. propofol, midazolam). Limited data is available on the specific effects of sedatives on QEEG trends in the cardiac arrest population, and unfortunately hourly sedation information for each patient is not available for the cohort in our study. If we had been able to account for effects of sedatives in training the model, this might have further improved prediction performance. Future studies should analyze and incorporate of specific effects of sedation in QEEG trends.

6) The performance of our time-sensitive model is modest (AUC=0.83), and our current modeling approach is not ready for deployment at the bedside. A model that can integrate initial clinical information and continuous EEG to other data streams such as serial clinical exams, brain imaging tests, sedation, serum biomarkers, and somatosensory evoked potentials has the potential to improve prediction performance beyond our current method.

CONCLUSIONS

We utilized a large, multi-center cohort with HIE to train a sequential prognostication model for good and poor functional outcomes. The QEEG model we developed is time-sensitive, selecting specific feature values at specific points in time that are most predictive of outcome. The time-sensitive model had better classification and statistical calibration compared to several state-of-the-art baseline approaches. These results demonstrate that the statistical association between quantitative EEG features and neurological outcome in HIE changes over time, and accounting for these changes improves performance of predictive models.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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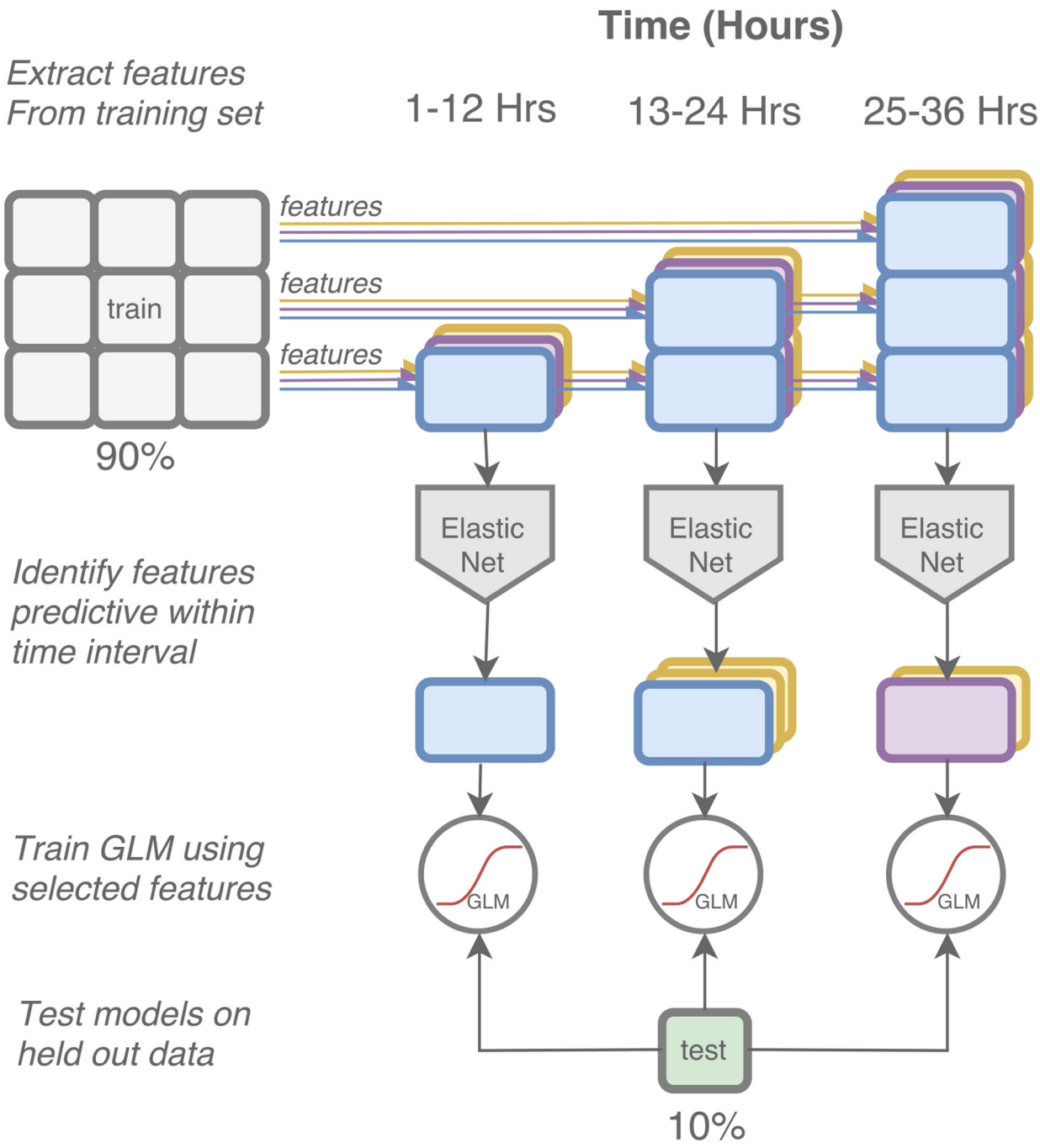

Figure 1: Modeling Approach

An overview of our modeling approach. Features (depicted as colored rectangles) are extracted from contiguous temporal partitions of our training data. All features within and preceding a given temporal partition are-provided to an Elastic Net regularized logistic regression model, which identifies the subset of features within the temporal partition most predictive of patient outcome. The selected features and training data are then used to generate a final general linear model (GLM) - the performance of which is evaluated on a held-out test set (green box).

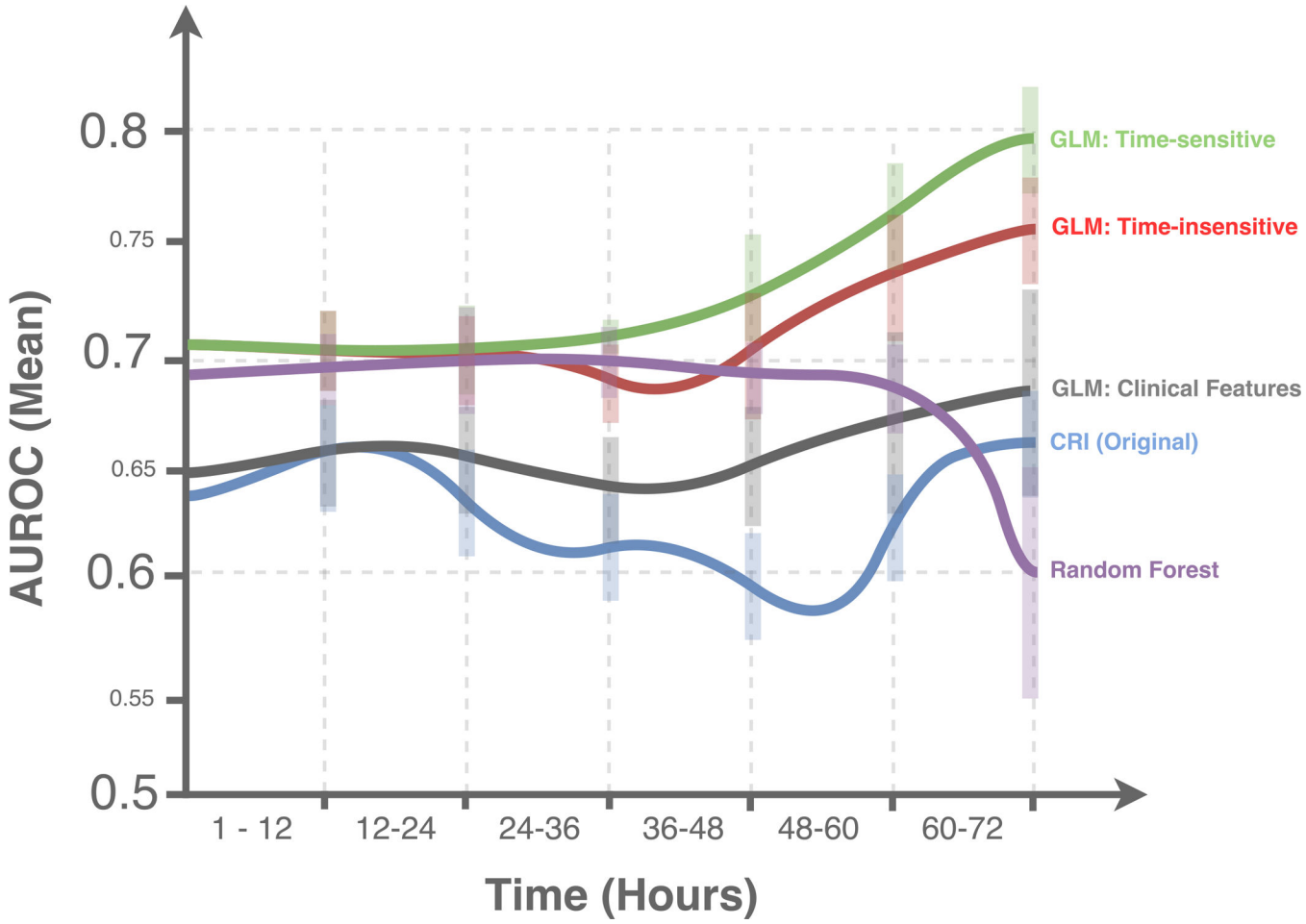

Figure 2: Model Performance Comparison as a Function of Time

A comparison of our time-sensitive (green) model's ten-fold Area Under the Receiver Operator Curve performance on the held-out testing sets over time and four baseline approaches: time-insensitive (red), the 2013 CRI (blue), Random Forest model inspired by the 2017 CRI (purple), and a model using four clinical features (age, gender, ROSC, and arrest rhythm) (gray).

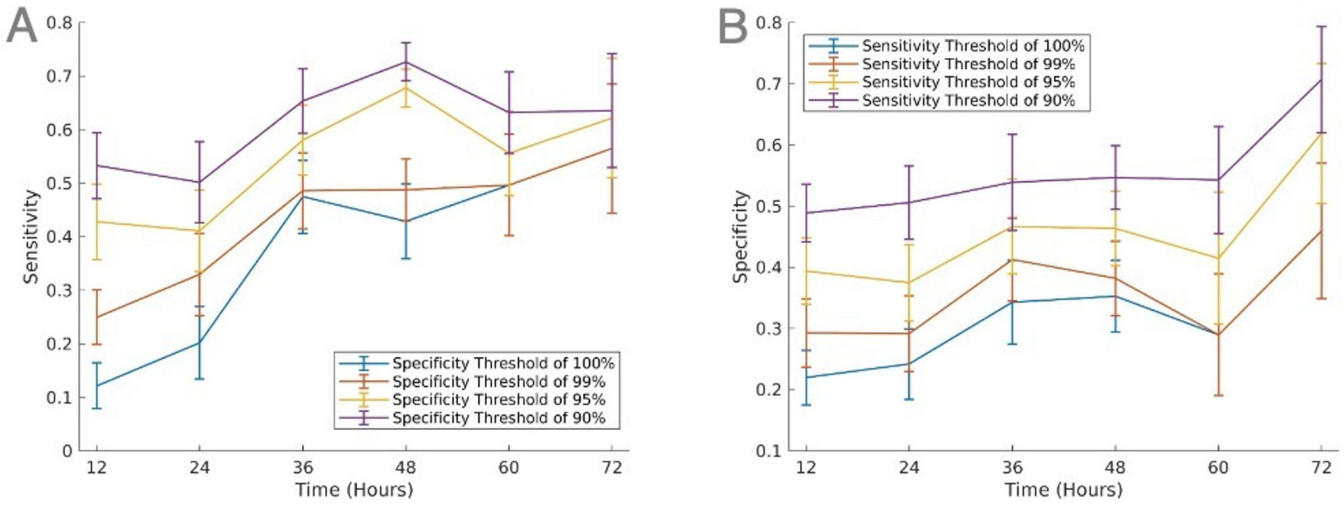

Figure 3: Specificity and Sensitivity of the Time-Sensitive Model at Different Sensitivity and Specificity Thresholds

(A) The mean specificity (and standard error) of the proposed approach at a variety of sensitivity thresholds of interest. (B) The mean sensitivity (and standard error) of the proposed approach at a variety of specificity thresholds of interest.

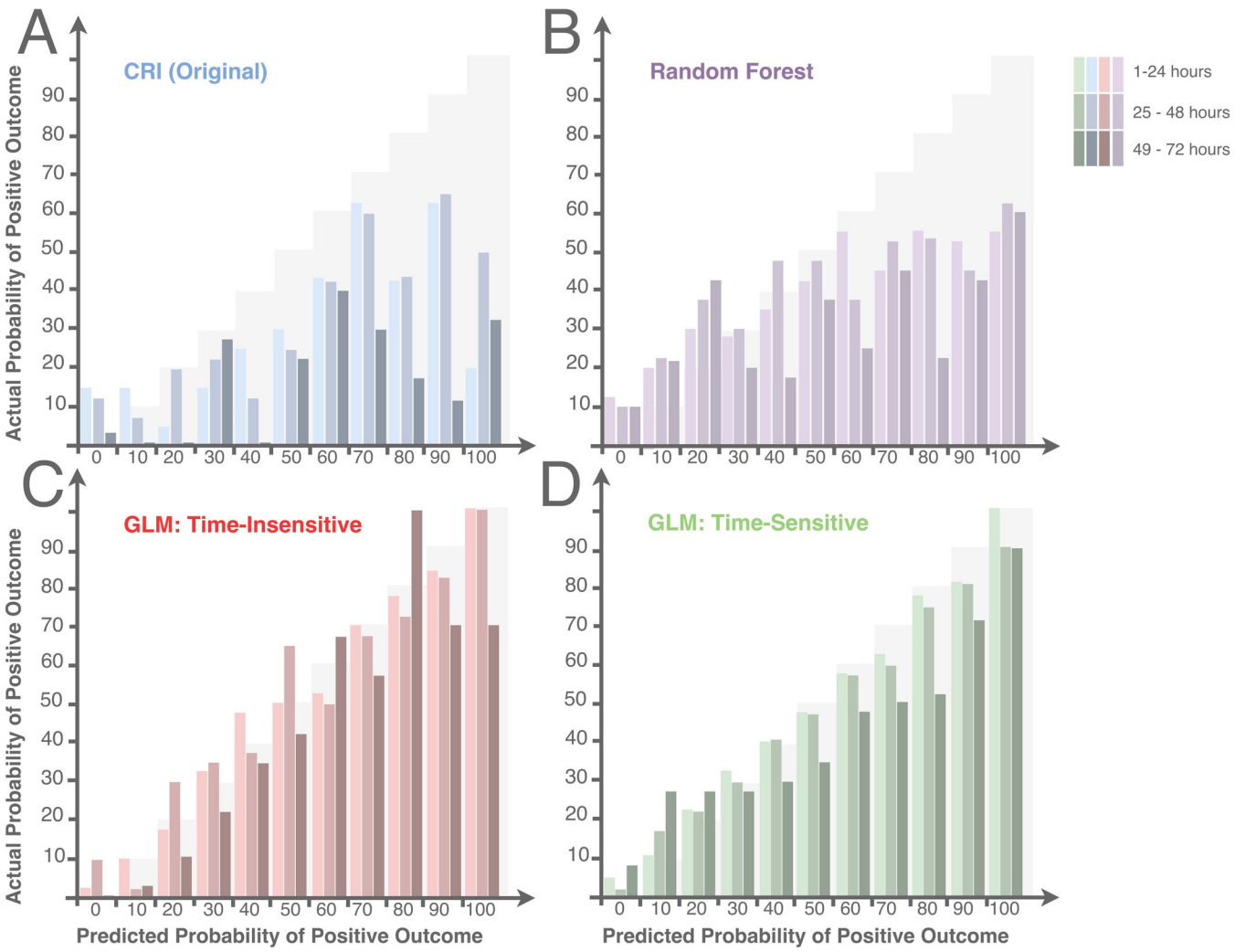

Figure 4: Model Calibration Performance Comparison for Each 24-hour Block.

A comparison of our model's calibration approach to three baseline approaches over three days post-cardiac arrest. Ideal calibration is achieved when colors bars perfectly overlap the gray shading in the background of each image. The calibration of a particular prediction level is shown as a bar. The shading of the bar reflects time (lighter is earlier, darker is later). (A) The calibration of the 2013 Coma Recovery Index (CRI); (B) the calibration of the Random Forest model based on the 2017 CRI; (C) the calibration of a time-insensitive logistic regression model; (D) the time-sensitive logistic regression model.

Table 1:

Collected Clinical information on patients, partitioned by CPC outcome

Variable	CPC 1 (N=111)	CPC 2 (N=23)	CPC 3 (N=9)	CPC 4 (N=14)	CPC 5 (N=281)
Age (years, mean)	53(16)	60(14)	68(13)	58(20)	62(17)
Gender (% male)	59	70	30	36	67
ROSC in minutes, (mean, std)	20(19)	14(12)	13(10)	13(8)	28(61)
Rhythm at Arrest					
Asystole (%)	5	13	10	7	18
PEA (%)	27	26	50	36	34
VFib (%)	41	17	10	21	14
VT (%)	7	4	0	7	3
Other (Non-VFib or VT) (%)	20	40	30	29	31
Cause of Arrest					
Cardiac (%)	23	4	10	29	18
Pulmonary (%)	5	13	10	7	12
Unknown (%)	6	0	0	0	2
Other/Unknown (%)	66	83	80	64	68
Arrest Location					
In-hospital (%)	18	30	50	0	10
Out-of-hospital (%)	35	17	0	43	40
Unknown (%)	47	53	50	57	50

CPC: Cerebral Performance Category; ROSC: Return of Spontaneous Circulation; PEA: Pulseless Electrical Activity; VFib: Ventricular Fibrillation; VT: Ventricular Tachycardia