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Prediction of patient survival following postanoxic coma using EEG data and clinical features

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Abstract— **Electroencephalography (EEG) is an effective and non-invasive technique commonly used to monitor brain activity and assist in outcome prediction for comatose patients post cardiac arrest. EEG data may demonstrate patterns associated with poor neurological outcome for patients with hypoxic injury. Thus, both quantitative EEG (qEEG) and clinical data contain prognostic information for patient outcome. In this study we use machine learning (ML) techniques, random forest (RF) and support vector machine (SVM) to classify patient outcome post cardiac arrest using qEEG and clinical feature sets, individually and combined. Our ML experiments show RF and SVM perform better using the joint feature set. In addition, we extend our work by implementing a convolutional neural network (CNN) based on time-frequency images derived from EEG to compare with our qEEG ML models. The results demonstrate significant performance improvement in outcome prediction using non-feature based CNN compared to our feature based ML models. Implementation of ML and DL methods in clinical practice have the potential to improve reliability of traditional qualitative assessments for postanoxic coma patients.**

I. INTRODUCTION

Over 550,000 North American adults suffer from cardiac arrest every year causing sustained injuries such as hypoxic ischemic encephalopathy (HIE). This condition has a high mortality rate, and causes mental and physical health damage to the patient and their families [1]. Despite advances in care, prognostication remains a difficult task that may suffer from inter-rater variability, necessitating the implementation of objective methods in assigning a recovery prediction for patients. Prognostic information can aid clinicians in selecting suitable treatment strategies and avoiding inappropriate cessation or continuation of life sustaining treatments [2].

Quantitative electroencephalography (qEEG) describes the algorithmic extraction of features from EEG data and may convey prognostic information associated with the severity of HIE and functional outcome. Past studies explore qEEG features extracted from time and frequency domains (e.g., amplitude, entropy, frequency power spectra) and demonstrate the importance of EEG background activity patterns (e.g., continuity, amplitude fluctuations) [3], [4]. Only a small number of studies leverage the advantages of information contained in clinical data by its inclusion in the feature set for machine learning (ML). Such studies are generally limited in the number of clinical variables available or are rarely analyzed in conjunction with qEEG [5], [6].

Deep learning (DL) approaches learn representations of data without relying on extracting predefined features, facilitating their use with raw biological signals such as EEG. As such, DL models can learn patterns and characteristics of the data essential to neurological outcome predictions as an automated pipeline free of heavy feature engineering. Amongst DL approaches, convolutional neural nets (CNNs) are extensively studied for their application in image and language processing and are used in many applications of EEG such as seizure prediction and emotion recognition [7], [8]. Since most of the information significant to clinical outcomes lies in the frequency domain, these approaches often convert the EEG signal to time-frequency domain spectrograms using short-time Fourier transform (STFT) which slides a window along the time-series performing frequency transformations to preserve the temporal characteristics of the signal, creating pseudo-images especially suited for CNN learning [7]. Despite the success of CNN models in various applications of EEG, its implementation for HIE prognosis is rare. Jonas et al. designed a CNN model for raw EEG signal based prognostication in comatose patients [9]. Spectrograms are commonly used for visual assessment and aid prognostication in clinical settings; to our knowledge, a spectrogram based CNN has not been evaluated in coma prognostication.

Due to the drawbacks of qualitative analysis of EEG, computer assisted interpretation can be used for a continuous assessment of EEG capable of discriminating between patients with various neurological outcomes. Specialists review clinical records along with EEG while determining prognosis; to reflect clinical prognostication practices, we use a unique combined dataset of qEEG and patient health records to determine HIE prognosis using ML models: random forest (RF) and support vector machine (SVM). Motivated by recent advances in deep learning EEG analysis, as well as lack of research in spectrogram based deep learning for HIE prognosis, we take a novel approach by using a spectrogram based CNN, avoiding the need for explicit feature engineering by using the intrinsic ability of the network to learn from data. We demonstrate that by combining clinical and qEEG features we improve the ability to predict patient outcome. We also show that spectrogram based CNNs are promising models for HIE prognostication that outperform feature based machine learning models.

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II. Materials and Methods

A. Data and preprocessing

We use a retrospective cohort study utilising clinically acquired routine EEG data for adults (male: 70, female: 31, age range: 19-87 years) diagnosed with cardiac arrest between January 2015 to September 2020 at the Kingston Health Sciences Centre. EEG are recorded for approximately 20-30 minutes as early as possible following the arrest with 21 scalp electrodes placed according to the 10-20 international system of electrode placement protocol. Only EEGs recorded in the first 8 days post arrest are used to reflect the typical time for patients to be transferred from external centres without EEG facilities for neuroprognostication. EEGs recorded during therapeutic hypothermia or containing significant artifacts through manual review are excluded and replaced with other EEG recordings of the same patient if available. Clinical data is collected retrospectively and ethics approval was obtained from the Institutional Research Ethics Board.

Functional outcome of the patients is evaluated using the Glasgow-Pittsburgh Cerebral Performance Category (CPC) scale [10] and was assessed at a followup rehabilitation appointment within 3-6 months. The CPC scores are dichotomized as 1-2 (good outcome, n=21) denoting patient survival post arrest with no more than moderate disability and CPC 3-5 (poor outcome, n=80) indicating severe disability, coma, or death.

Each EEG is band-pass filtered (0.5-70 Hz) and converted to an average referential montage where all electrodes excluding Fp1/Fp2 (eye blinks and eye movement artifacts) are used for average rereferencing. For each EEG recording, only the first clean 5-minute epoch is extracted for analysis. Preprocessing is performed using EEGLAB software [11] and MATLAB (Mathworks, MA, USA, R2019b).

B. Feature based prognosis of HIE

Extracted qEEG features and clinical features from medical records are used to train RF and SVM models to classify patient outcome. We extract 27 quantitative features as reported previously in the literature [3], [4], [5] described in Table I, and 9 clinical features: age, corneal and pupillary reflex, somatosensory evoked potential (SSEP), anoxic finding (CT, MRI), time from injury to EEG recording, cause of cardiac arrest (substance induced, arrhythmia, respiratory failure), type of cardiac arrest (ventricular fibrillation, pulseless electrical activity, ventricular tachycardia) and in/out of hospital arrest. All qEEG features are calculated per channel and averaged across channels to obtain a mean value per feature.

qEEG time domain features such as signal voltage, and standard deviation quantify statistical properties of the signal, while entropy, generally used in studies analyzing depth of anesthetics, represents the complexity and unpredictability of the signal [12]. Frequency domain features are extensively studied in outcome prediction problems; common features include absolute and relative power of frequency bands [5]. Power spectral density of each frequency band is estimated using Welch's averaged periodogram method with Hamming window and 50% overlap.

TABLE I: Extracted quantitative EEG features

Feature	Description
Time domain (5)	
Standard deviation	Measure of signal variability
Shannon entropy	Additive measure of signal stochasticity
Voltage spread	Low signal amplitude (3 levels: <5μV, <10μV, <20μV)
Frequency domain (18)	
Median power	Measure of variability
Absolute power	Spectral power in delta (0.5-4 Hz), theta (5-7 Hz), alpha (8-13 Hz), beta (14-20 Hz)
Relative power	Ratio between one band (delta-beta) and total power
Relative power of bursts	Spectral power of bursts (delta-beta)
Delta to alpha ratio	Delta power / alpha power
Sub-band information	Shannon entropy of each frequency band (delta-beta)
EEG background (4)	
Background continuity index	Fraction of EEG not in suppression (amplitudes<10 μV, >0.5 s)
Burst suppression amplitude ratio	Ratio of SD of the signal outside suppressions to that in suppressions
Number, length of bursts	Statistical properties of bursts

Due to high class imbalance (1:4), synthetic minority oversampling technique (SMOTE) [13] is used to increase the size of the minority class (good outcome) (1:1) to ensure the robustness and generalizability of results. Feature based min-max normalization is applied prior to classification. Parameter optimization of RF and SVM is conducted using grid search. Sequential floating forward selection (SFFS) [14] is used to select an optimal subset of features from the qEEG and clinical dataset to be used by the model.

C. Spectrogram based prognosis of HIE

To explore HIE outcome prediction without feature engineering, we propose the use of spectrograms and CNNs in lieu of feature based ML models. Raw EEGs are converted into spectrograms resembling a 2D image-like matrix containing frequency and time axes. For one 5-minute epoch available per patient, a sliding window length of 20 seconds is used to extract time-frequency information with a resolution of 1 Hz. To emphasize the clinical importance of lower frequencies and reduce the number of learnable parameters, only frequencies between 1 - 35 Hz are kept. To overcome the challenge of class imbalance we generate more spectrograms for the minority class by an increased overlapped sampling of the epoch during spectrogram creation. This is done by adjusting the overlap of the sliding window to 50% for poor outcome and 75% for good outcome (minority class).

As shown in Fig. 1, our CNN consists of 3 convolutional blocks (C1,2,3) each containing a convolutional layer with batch normalization, ReLU activation, and average pooling.

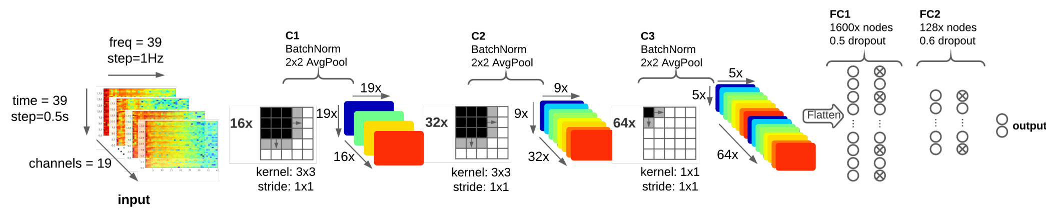


Fig. 1: Proposed convolutional neural network architecture depicting input and output dimensions, three convolutional blocks, and two fully connected layers

Batch normalization is added to increase the training stability, and pooling is added to extract features. Following the three convolutional blocks, we implement 2 fully connected layers (FC1,2), the output layer employs softmax activation function which exponentially normalizes the network outputs to present them as probabilities corresponding to the outcome classes. The model uses Adam optimizer, minimized categorical cross-entropy for loss, and early stopping is set to monitor validation loss. Our model is tuned with respect to the parameters such as STFT window length and overlap, learnable filters, hidden neurons, and layers.

The CNN classifies each spectrogram independently meaning the model evaluates a probability vector for each spectrogram indicative of poor outcome. However, since each patient has multiple spectrograms created from the 5-minute segment, the probability for an entire segment is obtained by averaging the probabilities of all spectrograms per patient. The 5-minute EEG segment is then classified as poor outcome if the average probability is above 0.5.

D. Experiments and evaluation

We compare the use of (1) qEEG features only, (2) clinical features only, and (3) the combination of both qEEG and clinical features using ML models: RF and SVM. We also compare the use of multichannel spectrograms as input to a CNN classifer against our qEEG RF and SVM models. To evaluate our RF$_{qEEG}$, RF$_{clinical}$, RF$_{qEEG+clinical}$, SVM$_{qEEG}$, SVM$_{clinical}$, SVM$_{qEEG+clinical}$, and CNN models, we use a 5-fold cross validation with different folding configurations (20 total models) to examine their performance. A holdout test set containing 20 patients (2500 spectrograms for CNN) is used for evaluation. Receiver operating characteristic (ROC) curves and area under ROC (AUROC/AUC) are used to assess model performance.

III. Results and Discussion

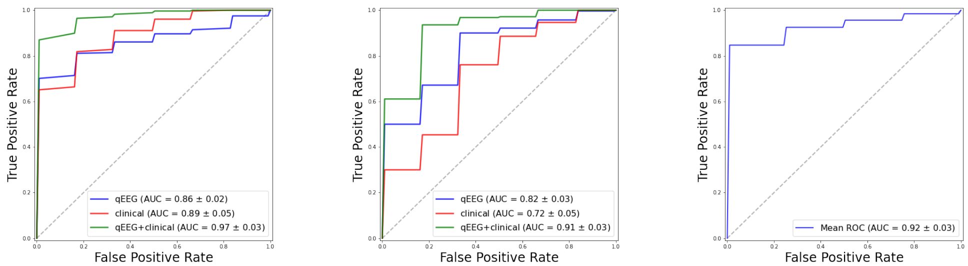
Table II shows performance metrics for RF, SVM and CNN models. The ROC curves depicting the true positive vs. false positive rates of the methods are in Fig. 2. According to Table II, both machine learning models using either of the feature schemes achieve high performance. However, performance is further improved using a combined set of qEEG and clinical features, SVM (AUC = 0.91) and RF (AUC = 0.97).

Prior to model evaluation, SFFS is used to select features best suited to improve the performance of the ML models. The 10 most significant features, from the combined 35 qEEG and clinical set, are selected that best contribute to the model's ability to predict clinical outcome. For Both qEEG+clinical machine learning models, SFFS selects similar features. For clinical features, RF selects type of cardiac arrest, SSEP and age, while SVM selects corneal reflex and SSEP. SSEP reflects the cortical response elicited by application of external stimuli, hence, its absence is associated with poor outcome. Previous studies also found that the absence of corneal reflexes post cardiac arrest is predictive of poor outcome [15]. Patient age is also a significant factor as younger groups are more likely to recover [10].

TABLE II: Model Performances

Model	Mean AUC (± SD)	Sensitivity
SVM$_{clinical}$	0.72 ± 0.03	0.81 ± 0.09
SVM$_{qEEG}$	0.82 ± 0.05	0.95 ± 0.05
SVM$_{qEEG+clinical}$	0.91 ± 0.04	0.90 ± 0.04
RF$_{clinical}$	0.89 ± 0.02	0.87 ± 0.07
RF$_{qEEG}$	0.86 ± 0.05	0.88 ± 0.03
RF$_{qEEG+clinical}$	0.97 ± 0.03	0.93 ± 0.02
CNN	0.92 ± 0.03	0.83 ± 0.06

The RF model selects qEEG features such as Shannon entropy, background continuity index, burst suppression amplitude ratio, and frequency features such as absolute delta power, as well as theta, delta, and alpha relative band powers. SVM selects Shannon entropy and frequency features such as median power, absolute delta and theta power, relative delta, theta, and alpha power as well as delta to alpha ratio (DAR). Features of EEG background prove their importance in numerous studies [3], [5]; consistently, studies find that a continuous EEG background post cardiac arrest predicts good outcome. Cortical synaptic activity (recorded by EEG) is interrupted post cardiac arrest and return of a continuous background indicates gradual recovery of synaptic activity. In addition, the degree of amplitude fluctuations is a significant predictor of poor outcome characterizing malignant patterns such as burst suppressions and generalized periodic discharges [3]. To provide an explanation, [3] suggests that an increase in excitatory-inhibitory ratio due to prolonged periods of anoxia causes excitotoxicity, secondary cell death, and subsequently poor outcome. Patients suffering from disorders of consciousness with improved outcome show greater EEG entropy than those with poor outcome, an increased entropy illustrates the increased complexity of cortical networks



(a) RF (b) SVM (c) CNN

Fig. 2: ROC curves and AUROC for models using 5-fold cross validation repeated four times (20 models). The blue line represents models with qEEG features, the red line represents ROC with clinical features, and green line represents a combined qEEG and clinical feature ROC.

required to support mechanisms of consciousness [12].

Features of frequency domain are well established for clinical prognosis [4], [5], [7]. EEG power is markedly affected in patients with HIE; a shift in spectral power towards lower frequencies is associated with prolonged comatose state and poor neurological outcome. Increased alpha is associated with good outcome and indicative of neural survival in ischemic regions of the brain. An increased delta power is seen in patients with poor outcome and reflects higher degree of brain lesions and deafferented regions. DAR is used to asses cortical ischemia with high DAR in patients with poor outcome. One hypothesis states DAR indicates the volume of brain tissue with pathophysiology [16].

Our results suggest that qEEG and clinical information serve as critical prognostic tools of HIE and their combined integration using ML outperforms our proposed individual feature set models. Recent studies show deep learning models prove new avenues for solving complex problems using EEG data. The AUC of our CNN model (0.92) exceeds that of RF (AUC = 0.86) and SVM (AUC = 0.82). Only a handful of studies implement CNNs for prognosis of HIE comatose patients. Jonas et al. achieves an AUC of 0.89 using raw EEG signals with CNNs [9] . A major difference in our work is the use of time–frequency information as input to our CNN model outperforming our proposed ML models with qEEG features. In contrast to feature based ML systems, a deep learning model such as CNN can be utilized without the need for a feature extraction strategy.

IV. Conclusion

In this paper, the performance analysis of machine learning models, RF and SVM, in predicting HIE outcome is carried out using a novel dataset combining qEEG and clinical information to reflect clinical prognostication protocols. This combinatorial approach outperforms models using individual feature types. The results of qEEG machine learning models are compared to the proposed non-feature based CNN. We show how the CNN architecture can be applied to spectrograms derived from EEGs to predict HIE outcome. The model achieves comparable accuracy to state-of-the-art HIE outcome models as well as outperforming our proposed qEEG ML models. This system of automatic feature extraction is advantageous over manually crafted feature approaches and can be further analyzed through the integration of clinical data into the DL model.

References

[1] P. A. Meaney et al., "Cardiopulmonary Resuscitation Quality: Improving Cardiac Resuscitation Outcomes Both Inside and Outside the Hospital," Circulation, 128(4): 417–435, 2013.
[2] C. H. Duez et al., "Large inter-rater variability on EEG-reactivity is improved by a novel quantitative method," Clinical Neurophysiology, 129(4): 724–730, 2018.
[3] B. J. Ruijter, J. Hofmeijer, M. C. Tjepkema-Cloostermans, and M. J. A. M. van Putten, "The prognostic value of discontinuous EEG patterns in postanoxic coma," Clinical Neurophysiology, 129(8): 1534–1543, 2018.
[4] M. C. Tjepkema-Cloostermans, F. B. van Meulen, G. Meinsma, and M. J. A. M. van Putten, "A Cerebral Recovery Index for early prognosis in patients after cardiac arrest," Critical Care, 17(5), 2013.
[5] M. M. Ghassemi et al., "Quantitative Electroencephalogram Trends Predict Recovery in Hypoxic-Ischemic Encephalopathy*," Critical Care Medicine, 47(10): 1416–1423, 2019.
[6] D. S. O'Boyle et al., "Improvement in the Prediction of Neonatal Hypoxic-Ischemic Encephalopathy with the Integration of Umbilical Cord Metabolites and Current Clinical Makers," The Journal of Pediatrics, vol. 229, 2021.
[7] N. D. Truong et al., "Convolutional neural networks for seizure prediction using intracranial and scalp electroencephalogram," Neural Networks, 105: 104–111, 2018.
[8] H. Mei and X. Xu, "EEG-based emotion classification using convolutional neural network," 2017 International Conference on Security, Pattern Analysis, and Cybernetics (SPAC), 2017.
[9] S. Jonas, A. O. Rossetti, M. Oddo, S. Jenni, P. Favaro, and F. Zubler, "EEG-based outcome prediction after cardiac arrest with convolutional neural networks: Performance and visualization of discriminative features," Human Brain Mapping, 40(16): 4606–17, 2019.
[10] C. Sandroni, S. D'Arrigo, and J. P. Nolan, "Prognostication after cardiac arrest," Critical Care, 22(1), 2018.
[11] A. Delorme and S. Makeig, "EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis," J. Neuroscience Methods, 134(1): 9–21, 2004.
[12] Z. Liang, et al., "EEG entropy measures in anesthesia," Frontiers in Computational Neuroscience, vol. 9, 2015.
[13] N. V. Chawla, K. W. Bowyer, L. O. Hall, and W. P. Kegelmeyer, "SMOTE: Synthetic Minority Over-sampling Technique," Journal of Artificial Intelligence Research, 16:321–357, 2002.
[14] M. C. Baker, A. S. Kerr, E. Hames, and K. Akrofi, "An SFFS technique for EEG feature classification to identify sub-groups," 2012 25th IEEE Int. Sym. Computer-Based Medical Systems (CBMS), 2012.
[15] N. A. Chiota, W. D. Freeman, and K. M. Barrett, "Hypoxic-Ischemic Brain Injury and Prognosis After Cardiac Arrest," CONTINUUM: Lifelong Learning in Neurology, 17:1094–1118, 2011.
[16] J. Leon-Carrion, J. F. Martin-Rodriguez, J. Damas-Lopez, J. M. Barroso y Martin, and M. R. Dominguez-Morales, "Delta–alpha ratio correlates with level of recovery after neurorehabilitation in patients with acquired brain injury," Clinical Neurophysiology, 120(6): 1039–1045, 2009.