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Machine Learning Analysis of Heart Rate Variability for the Detection of Seizures in Comatose Cardiac Arrest Survivors

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ABSTRACT Objective: Heart rate variability (HRV) reflects autonomous nervous system disturbance and is used for seizure prediction. The aim of this study was to develop a real-time, continuous physiological medical signal data acquisition system in seizure detection for intensive care unit (ICU). Methods: This prospective study was conducted in National Taiwan University Hospital from August 2018 to October 2019. This study included 20 patients who (a) had a sustained return of spontaneous circulation following out-of-hospital cardiac arrest, (b) were over 18 years old, (c) and were admitted to the emergency ICU for post-cardiac-arrest care. One-lead electrocardiography and bilateral two-channel electroencephalography recorders were synchronically used to conduct measurements for a maximum of 72 hours. The recorded data were wirelessly real-time transmitted by a proxy transmitting module through an access point and a local gateway. A system with a novel algorithm processed the signals and conducted feature extraction and supervised learning for seizure detection. Results: A total of 89 nonseizure and 83 seizure events were detected by the system. Seizure occurred in two-thirds of the patients assessed by intensivists and neurologists. Four HRV parameters, namely standard deviation of normal-to-normal R-wave intervals, high frequency, low frequency–high frequency ratio, and sample entropy, were determined as potential features for identifying seizures. The sensitivity and specificity of the developed system were 0.74 and 0.81, respectively, and the positive predictive value was 0.82. Conclusion: The developed system can be used to identify seizure events through HRV features. Significance: The current study achieved real-time seizure detection and overcame previous limitations on continuity and accessibility.

INDEX TERMS Heart rate variability, seizure, cardiac arrest, machine learning, electroencephalography.

I. INTRODUCTION

Out-of-hospital cardiac arrest (OHCA) is a global public health concern, with 420,000, 270,000, and 220,000 cases being annually reported in the United States, Europe, and Asia, respectively [1]–[3]. Overall, the average survival-to-discharge rate is less than 20% following cardiopulmonary resuscitation (CPR) [2]. Even after survival, patients may develop severe neurological sequela, which increases their medical costs for long-term care and decreases their quality of life. Post-cardiac arrest syndrome (PCAS), a multiple pathophysiological process, involves multiple organs and is associated with poor clinical outcomes. According to the database of the Canadian Critical Care Research Network, more than 60% of Canadian patients admitted to intensive care units (ICUs) after cardiac arrest have PCAS [4], with similar incidence rates being observed in the United Kingdom (71%) [5] and Japan (90%) [6]. PCAS includes brain injury, myocardial dysfunction, and systemic ischemia or reperfusion response. Brain injury is a common cause of morbidity and mortality, and it affects 68% of cardiac arrest survivors [7]. The complications of brain injury include seizures, strokes, and brain death. Pathophysiologically, the lack of cerebral oxygenation during the ‘‘no-flow’’

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time results in the loss of ATP production and the dysfunction of membrane-ATP-dependent Na-K pumps. The subsequent loss of cellular integrity triggers the release of glutamate, which causes excitotoxic injury; this is mainly mediated by N-methyl-D-aspartate receptors [8].

Seizures, which are defined as sudden and uncontrolled electrophysiological disturbances in the brain, occur more frequently in cardiac arrest survivors than other complications, such as diabetes insipidus and coagulopathy. In the acute stage of post-cardiac arrest, patients experience convulsive seizures, nonconvulsive seizures, or status epilepticus, with incidence rates ranging from 8% to 60% [9]. Cardiac arrest survivors experiencing seizure episodes may have poor prognosis [10]. Managing comatose and heavily sedated patients is difficult. Easily ignored, dangerous, and implicit signs may increase the mortality rate for patients experiencing seizures after the return of spontaneous circulation (ROSC). An early seizure alarm system can enable a caregiver to take appropriate action, including clearing the airway; providing oxygenation; ensuring protection against physical injuries; and administering prophylactic antiepileptic drugs, such as carbamazepine, phenytoin, or valproate, if required [11]. The earlier a seizure is detected or predicted, the better is the prognosis of the patient.

Electroencephalography (EEG; a noninvasive, real-time method) can be used to measure the cortical electrical activity of the brain. This technique is widely used in epilepsy research and diagnosis [12]–[14]. However, the aforementioned technique is associated with some limitations related to accessibility. It only records the moment of seizure episodes and cannot predict them. Some patients may develop skin abrasions due to the prolonged application of surface electrodes. The traditional setup of 20 electrodes on the skull may be time consuming and may increase the medical cost. The use of the electrode setup increases the care burden, especially for critical patients. Furthermore, the aforementioned setup provides a low signal-to-noise ratio (SNR), which results in poor signal quality due to the lack of metal shielding protection and may increase the medical burden. Clinically, EEG is still the gold standard for diagnosing seizures; however, a surrogate diagnostic tool is becoming popular for the detection and prediction of seizures.

Recently, the communication between the brain and the heart has drawn research attention [15]. Heart rate variability (HRV) signals may enable the prediction of seizures [13], [16]–[21]. HRV reflects the activity of both parts of the autonomic nervous system (ANS). HRV can be calculated by determining the difference between each R-wave in electrocardiography (ECG). Abnormal neuronal electrical activity corresponding to a seizure can involve central centers for the regulation of autonomic activity, which causes dysautonomia. Power spectral analysis of HRV signals may provide valuable information prior to seizure episodes [22]. The main advantage of power spectral analysis includes its simplicity in postprocessing of low- and high-frequency powers of HRV. HRV parameters are decoded from the ECG signals. ECG signals (order of millivolts) have a larger amplitude than EEG signals (order of microvolts). The SNR is higher in ECG-based measurement than in EEG-based measurement. ECG-based HRV can be recorded on a single channel, and the recording is continuously accessible in each patient admitted to the ICU. Behbahani *et al.* (2013) found that increased sympathetic heart rate modulation and decreased vagal heart rate modulation often precede ictal EEG changes in temporal lobe seizures [23]. Moridani *et al.* (2017) indicated that epileptic seizures are associated with an increased heart rate, which suggests an increased sympathetic tone and a reduced vagal tone. The HRV-based seizure prediction algorithm of Moridani *et al.* achieved 88.3% sensitivity and 86.2% specificity in 11 epilepsy patients. HRV may reflect EEG changes in advance. Fujiwara *et al.* used a wearable sensor to record and analyze HRV for developing an HRV-based epileptic seizure prediction method [13]. In the aforementioned studies, the EEGs were intermittently recorded due to the limitation of medical facilities. The previous methodology not only fails to timely detect seizure events but also has limited prediction ability.

A real-time, continuous monitoring system that can access and analyze specific physiological signals is required for application in practical critical care. The aim of this study was to develop a real-time, continuous physiological medical signal data acquisition (PMSDA) system for ICU applications. The developed system provides an easily accessible network platform for the recording of ECG and EEG biosignals. EEG signals are processed through signal decomposition, threshold value determination, and evaluation by a neurologist. Moreover, ECG feature extraction is performed simultaneously with EEG processing.

Machine learning analysis provides a prediction of clinical outcomes, whereas traditional statistical analysis infers relationships between variables or discovers insights. Machine learning identifies generalizable predictive patterns; however, statistical analysis involves making population-level inferences from a small sample. Machine learning analysis can be used to analyze "wide data," in which the number of input variables exceeds the number of subjects [24]. The aim of this study was to predict potential seizure occurrence in comatose cardiac arrest survivors on the basis of biosignals. In this study, the prediction capability for seizure was more important than the identification of risk factors for seizure. Moreover, "wide data" were adopted. Therefore, machine learning analysis was adopted, and supervised machine learning of the aforementioned biosignals was performed. The correlation between HRV features and seizures was then identified.

II. MATERIALS AND METHODS

A. STUDY DESIGN AND PATIENT RECRUITMENT

This single-center, prospective cohort study was approved by the Institutional Review Board of National Taiwan University

Hospital (NTUH) (number: 201711011RINC) and was registered at ClinicalTrials.gov. Informed consent was obtained from the patients' families. This study included patients who (a) had sustained ROSC following OHCA, (b) were older than 18 years, (c) and were admitted to the emergency ICU (EICU) for postcardiac arrest care. Patients were excluded if they (a) had traumatic OHCA, (b) had a history of traumatic brain injury confirmed by previous computed tomography or medical records, (c) had medical documentation of spontaneous nontraumatic intracerebral hemorrhage, (d) had a history of brain surgery, (e) were brain dead, and (f) were pregnant (if female). A total of 23 patients were initially recruited between August 2018 and October 2019. Among the patients, two refused to participate in the measurement and were excluded. One patient passed away within 1 h. Data could not be recorded for this patient, so the patient was excluded. The remaining 20 patients completed the study protocol and were eligible for the final analysis.

B. DATA RECORDING, EXITRACTION, AND ANALYSIS

Figure 1 displays the environmental setting in the EICU. Ten ICU beds are available for patients in the limited space. One-lead ECG (simplified lead II mode) and bilateral two-channel EEG (four sensors with one reference node) recorders were placed on each patient. EEG and ECG signals were recorded synchronically and continuously for a maximum of 72 h since EICU admission. The hardware platform of the PMSDA system consisted of surface sensors, a front-end device, a network complex, and a data transfer station. After the physiological data were recorded by the front-end device through different types of sensors, the data were wirelessly transmitted by a proxy transmitting module through an access point (AP) and a local gateway. NPort W2250A (MOXA, Taiwan) was connected to the data export port of a central monitor (IntelliVue MX800®, Philips) through a serial cable with a baud rate of 115200. The exported data were real-time and synchronously transmitted to an AP/repeater named D-Link N300 (D-Link, Taiwan), which had a maximum wireless speed of 300 Mbps and

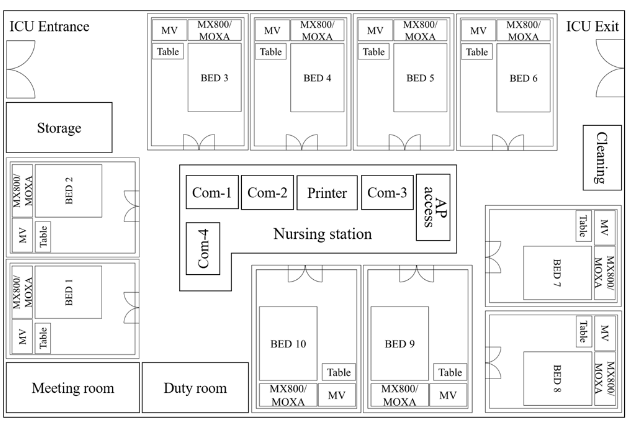

FIGURE 1. General layout of the emergency intensive care unit. The beds are separated into different isolated areas for patient care.

an antenna gain of 5 dBi. A computer served as the data collection and preprocessing center for collecting all nodes of the network and for synchronization with the vital signs monitor screen of the central monitor for each patient. The raw data, including ECG and EEG signals, were decoded as a text file. MATLAB (MathWorks, Inc.) was used for waveform construction, characteristic extraction, and signal processing (Figure 2).

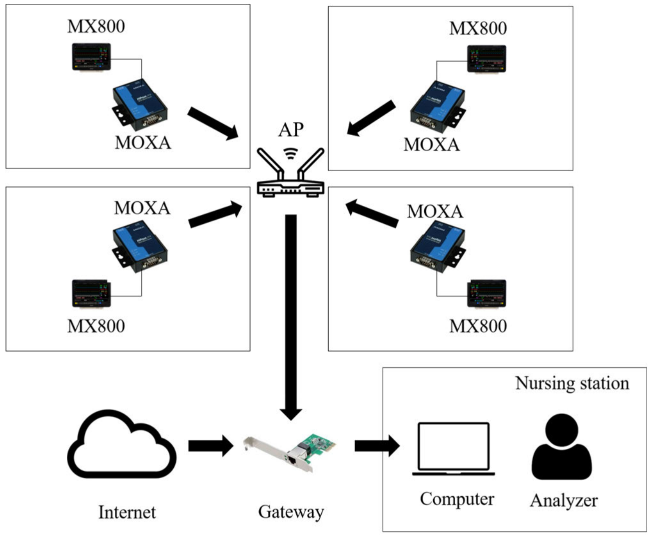

FIGURE 2. Hardware of the data collection system.

C. HRV

Figure 3 depicts the block diagram of the study design. The bottom level (level I) shows the patient recruitment. A patient who meets the inclusion criteria is eligible. Both EEG and ECG signals are recorded and extracted for further processing. Level II displays the processing procedure for ECG (left-sided dashed line box) and EEG (right-sided dashed line box) signals. For ECG processing, the R–R interval (RRI) of the ECG signal was defined as the interval between one R-wave and the next R-wave. The sampling frequency was 250 Hz, and the operating voltage was 5 V. The frequency in the filter was 0 to 0.4 Hz. HRV analysis was categorized into time, frequency, and nonlinear analyses. In time-domain analysis, R–R mean interval, standard deviation of normal-to-normal (SDNN) intervals, root mean square of successive differences (RMSSD), number of differences in consecutive RRIs greater than 50 ms (NN50), and ratio of the total number of NN50 intervals to RRIs (pNN50) were calculated [25]. Frequency-domain analysis of HRV reflects the ANS function and is widely used in clinical practice. A fast Fourier transform is an algorithm that computes the discrete Fourier transform of a sequence.

$$Y_k = \sum_{t=0}^{N-1} y(t)\, e^{-i\frac{2\pi}{N}kt}, \quad K = 0, 1, 2, \ldots\ldots N-1 \quad (1)$$

Frequency-domain analysis was performed initially through fast Fourier transformation. The power of each

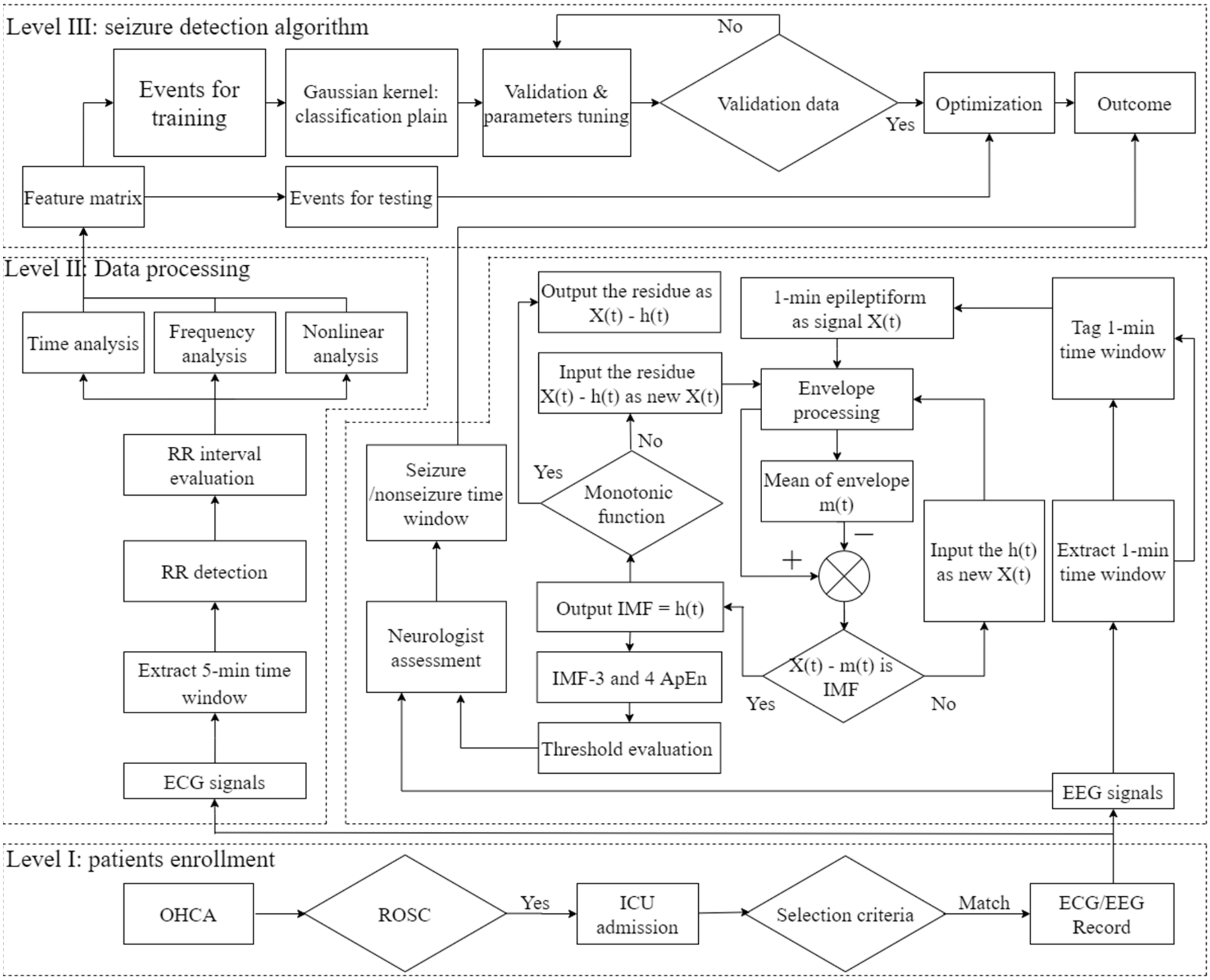

FIGURE 3. Block diagram of the study design, which includes patient recruitment, data extraction, data analysis, and the seizure detection algorithm.

frequency band, including the total power (TP), very low frequency (VLF), low frequency (LF), high frequency (HF), and LF to HF ratio (LF/HF), was then calculated [26]. The frequency ranges of the TP, VLF, LF, and HF were 0–0.4, 0.0033–0.04, 0.04–0.15, and 0.15–0.4 Hz, respectively. The TP reflects all potential physiological mechanisms. The VLF reflects slow mechanisms of sympathetic activity. The LF is generally a significant indicator of sympathetic activity [27]. The power spectral density (PSD) describes how the power of a signal or time series is distributed with frequency. The power of a signal in a given frequency band can be calculated by integrating the frequency values of the band. The PSD is expressed as follows:

$$\varphi(\omega) = \sum_{t=-\infty}^{\infty} r(t)e^{-i\omega t} = \lim_{N\to\infty} E\left[\frac{1}{N}\left|\sum_{t=0}^{N-1} y(t)e^{-i\omega t}\right|^2\right] \tag{2}$$

where E denotes the expected value.

In nonlinear analysis, Poincaré return maps, which are used for analyzing HRV nonlinear dynamics, graphically display the correlation between consecutive RRIs [28]. Poincaré mapping provides useful information on short- and long-term fluctuations. The parameters SD_1 and SD_2 are also calculated. SD_1 refers to the rapid beat-to-beat changes, which are related to respiratory sinus arrhythmia, and SD_2 describes long-term beat-to-beat changes.

The unpredictability of the RRIs can be calculated from the ratio of SD_1 to SD_2. Physiologically, the aforementioned ratio reflects the ANS balance once sympathetic activation occurs during a long period of observation [29].

$$SD_1 = 0.7 \times SD(RR_{n+1} - RR_n) \tag{3}$$

$$SD_2 = \sqrt{2 \times SD(RR_n)^2 - 0.5 \times SD(RR_{n+1} - RR_n)^2} \tag{4}$$

where RR_{n+1} refers to the $(n+1)^{th}$ beat-to-beat interval, RR_n represents the n^{th} beat-to-beat interval, and SD denotes the standard deviation. The SD_1-to-SD_2 ratio is also correlated with the LF/HF ratio [30].

Entropy measures have been used to assess the regularity or predictability of fluctuations over time-series data [31]. Two commonly used entropy measures are approximate entropy (ApEn) and sample entropy (SampEn). ApEn quantifies the amount of regularity and the unpredictability of fluctuations over time-series data. SampEn reduces the bias of self-comparisons. It can be regarded as a variation of ApEn. Both SampEn and ApEn have been widely used to relate clinical disorders with physiological and pathological conditions [32].

D. EMPIRICAL MODE DECOMPOSITION AND APPROXIMATE ENTROPY

Empirical mode decomposition (EMD) is the first step in EEG processing, as depicted in Figure 3 (right-sided dashed box in level II). The EMD method is based on the assumption that any nonstationary and nonlinear time series consists of different simple intrinsic modes of oscillation. The core concept of EMD is to empirically identify these intrinsic oscillatory modes according to their characteristic time scales and then decompose them appropriately [33]. EMD involves operations that partition a series into several intrinsic mode functions (IMFs) without leaving the time domain (sifting process) [34]. Each IMF is a monotonic function with a unique frequency band.

$$\mathrm{x}\left(\mathrm{t}\right) = \sum\nolimits_{n} x_n\left(t\right) + r(t) \tag{5}$$

The average of the upper and lower envelopes of a signal X(t), namely Mn(t), can be derived through cubic-spline interpolation. The first component (H_1) is expressed as follows: $H_1(t) = X(t) - M_1(t)$. The following component is obtained by repeating the aforementioned processing. The parameter $r_n(t)$ is defined as the n^{th} difference between the input signal and the n^{th} IMF. If $r_n(t)$ is a monotonic function, EMD is terminated and IMFs are obtained. Otherwise, $r_n(t)$ is regarded as the input signal for the next loop to generate the $(n + 1)^{th}$ IMF [33].

Ramakrishnan *et al.* found that IMF-3 and IMF-4 efficiently distinguish between seizure and nonseizure events [35]. Because ApEn is an entropic measure to quantify the regularity of medical data, it serves as an index for the judgment of seizure events [32]. The EEG waveform was first composed from the raw data and then decomposed into several IMFs. The ApEn of IMF-3 and IMF-4 was calculated. The threshold value was determined to detect seizures. Moreover, the EEG waveform was reviewed by an independent neurologist. A seizure event was defined according to both the IMF value and neurologist's assessment.

E. DETECTION MODEL TRAINING ALGORITHM

An excellent binary classifier is essential for distinguishing seizure status from nonseizure status. Support vector machine (SVM), which is a supervised machine learning method, was used as a classifier in this study to develop a detection model, especially for linearly nonseparable data. SVM uses a technique called the kernel function to transform data. The kernel function maps the input space into a higher-dimensional linear separable feature space and thereby provides an optimal boundary between possible outputs. Theoretically, the main purpose of SVM is to find a hyperplane in an N-dimensional space that distinctly classifies the data points [36]. In the developed system, hyperplanes are multidimensionally selected to aid the classification of the outputs (seizure or nonseizure events) [37]. HRV parameters were the input features, and the optimal combination of characteristics was determined through SVM. Compared with other machine learning algorithms, SVM provides superior generalization capabilities for the classification of biosignals in the developed system by minimizing structural and empirical risks [38], [39], even for a relatively small training dataset that originates from a specific study population (comatose cardiac arrest survivors). SVM has been widely used for applications in seizure detection [40].

Moreover, leave-one-out cross validation was used to validate the model. Leave-one-out cross validation is a special case of cross validation in which the number of folds equals the number of instances in the dataset [41]. This type of cross validation is mainly used in the case of a small sample size.

F. OUTCOMES

The primary and secondary outcomes of this study were in-hospital mortality and neurological recovery at hospital discharge, respectively. Neurological recovery was clinically assessed by attending physicians according to Glasgow–Pittsburgh Cerebral Performance Category (CPC) scores, where CPC scores of 1 or 2 indicated satisfactory neurological function and CPC scores of 3 to 5 indicated poor neurological outcome [42]. The presentation of clinical convulsion was assessed by intensivists, who administered antiepileptic drugs (AEDs) if a seizure episode was suspected.

For examining the sensitivity and specificity of the model, an independent neurologist, who was clinically blinded and did not serve the patients and manage the data, carefully reviewed the EEG waveform constructed from the raw data. Using the EEG waveform, the neurologist determined whether the waveform represented a seizure pattern. Waveforms composed of artificial noise or other waveforms were considered as nonseizure patterns.

G. STATISTICAL ANALYSIS

The Shapiro–Wilk test, which was proposed by Samuel Sanford Shapiro and Martin Wilk in 1965, examines if a variable is normally distributed in a population [43]. The nonparametric method is used if a variable is not normally distributed. Continuous variables with normal distributions are presented as mean ± standard deviation. These variables were compared between seizure and nonseizure groups by using Student's t test. Categorical variables are presented as numbers (percentages), and these variables were compared using the chi-squared test (χ^2 test). Fisher's exact test was performed toward small mathematical expectation. Statistical significance was set at $p \leq 0.05$. Statistical analyses were conducted using SAS (version 9.4, SAS Institute, Chicago, IL, USA). All figures were plotted using SigmaPlot (Systat Software, Inc.).

III. RESULTS

The baseline characteristics of the enrolled patients are presented (Table 1). A total of 20 eligible patients were admitted to the EICU for post-cardiac arrest care. Of these patients, 13 (65%) were men. The age of the patients ranged from 46 to 86 years. Sepsis complicated with septic shock was the major cause of cardiac arrest (52%), followed by respiratory system failure (33%). Targeted temperature management, which achieved good neurological outcomes by minimizing cerebral energy consumption, was administered to 17 patients (81%). Seizures occurred in two-thirds of the patients clinically assessed by intensivists. Almost 80% of the patients received AEDs, including levetiracetam, phenytoin, or valproic acid, when seizures occurred. Eight patients (39.1%) survived after the treatment course; however, all patients failed to achieve good neurological recovery, and their CPC score was more than 3.

ECG and EEG data were extracted and analyzed (Figure 3, level II). The duration of each normal-to-normal heart beat was calculated by subtracting the time difference between consecutive RRIs. A noise filter was used to eliminate potential interference. Figure 4(a) and 4(b) illustrate the 5-minute measurements of the RRIs (in milliseconds) for nonseizure and seizure events, respectively. After transformation, the PSD of each frequency band was calculated

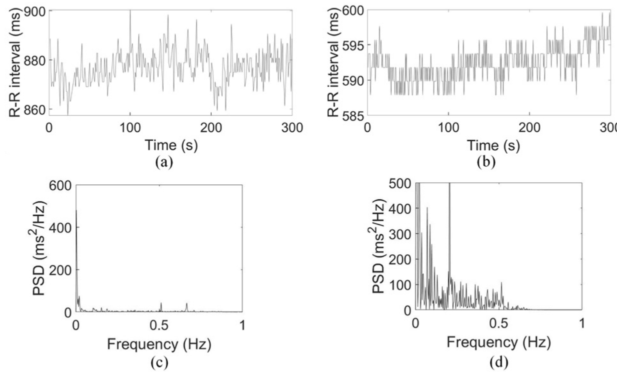

FIGURE 4. **The extraction of R-R interval of heart rate variability (HRV) in (a) nonseizure and (b) seizure event, and power spectrum of HRV in frequency domain in (c) nonseizure and (d) seizure event.**

[Figure 4(c) (nonseizure) and Figure 4(d) (seizure)]. The PSD of seizure events was higher than that of nonseizure event at LF, HF, and the TP (area under the curve). Moreover, the IMFs were decomposed through EMD, as illustrated in Figure 5 and Figure 6. The EEG amplitude of seizure events was significantly higher than that of nonseizure events. Because IMF-8 in the seizure events was a monotonic function, IMF-9 was not extracted (Figure 6). The threshold value was 0.15 for IMF-4 and 0.2 for IMF-3. The events were separated into two subgroups according to the threshold value. The EEG waveforms in these subgroups were sequentially evaluated by a neurologist.

A comparison of the HRV parameters between seizure and nonseizure events is presented (Table 2). A total of 83 signals were extracted before and during seizure events, whereas 89 signals were extracted and were considered to represent

TABLE 1. **The baseline characteristics of the enrolled patients.**

Patients no.	AGE (YEARS)	Sex	CA cause	TTM	Record duration (hours)	Seizure	AED use	AED type	IN-HOSPITAL MORTALITY	CPC
1	86	F	Respiratory	Y	27.2	Y	Y	Lev	Y	5
2	79	F	Respiratory	Y	11.8	Y	Y	Lev, Phe, Val	Y	5
3	59	M	Respiratory	Y	25.5	Y	N		Y	5
4	47	M	Respiratory	Y	57.1	Y	Y	Lev	Y	5
5	68	F	Sepsis	N	27.2	N	N		Y	5
6	77	F	Sepsis	Y	31.9	Y			Y	5
7	78	M	Sepsis	N	21.8	N	N		Y	5
8	63	F	Sepsis	Y	68.9	Y	N		N	4
9	70	F	Cardiac	Y	53.7	N	N		Y	5
10	65	M	Sepsis	Y	72.0	Y	Y	Val	Y	5
11	62	M	Sepsis	Y	72.0	N	N		N	3
12	66	M	Cardiac	Y	53.4	Y	Y	Lev	Y	5
13	81	M	Respiratory	Y	50.0	Y	Y	Lev	Y	5
14	46	F	Sepsis	Y	67.8	N	N		N	4
15	64	M	Sepsis	Y	49.7	Y	Y	Lev	Y	5
16	77	M	Respiratory	N	8.2	N	N		N	5
17	71	M	Sepsis	Y	48.1	Y	Y	Lev, val	N	5
18	72	M	Cardiac	Y	72.0	Y	N		N	5
19	51	M	Sepsis	Y	72.0	Y	N		Y	4
20	76	M	Respiratory	Y	36.2	Y	Y	Val	N	5

AED = anti-epileptic drugs; CA = cardiac arrest; CPC = cerebral performance category; Lev = Levetiracetam; Phe = Phenytoin; TTM = therapeutic temperature management; Val = Valproic acid.

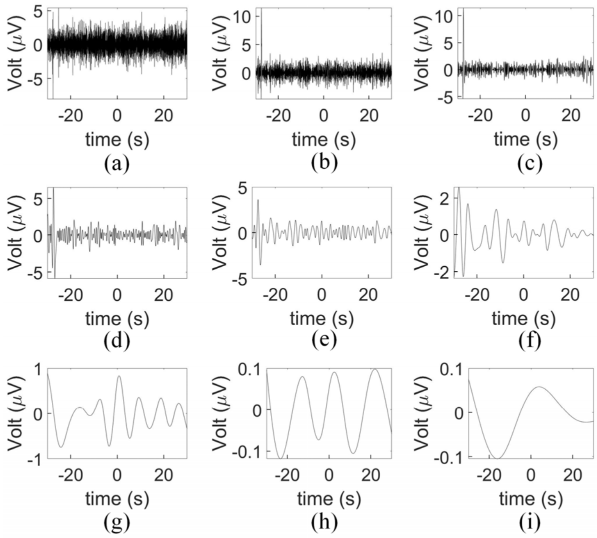

FIGURE 5. Intrinsic mode functions (IMFs) extraction in a nonseizure event: (a) IMF-1; (b) IMF-2; (c) IMF-3; (d) IMF-4; (e) IMF-5; (f) IMF-6; (g) IMF-7; (h) IMF-8; (i) IMF-9.

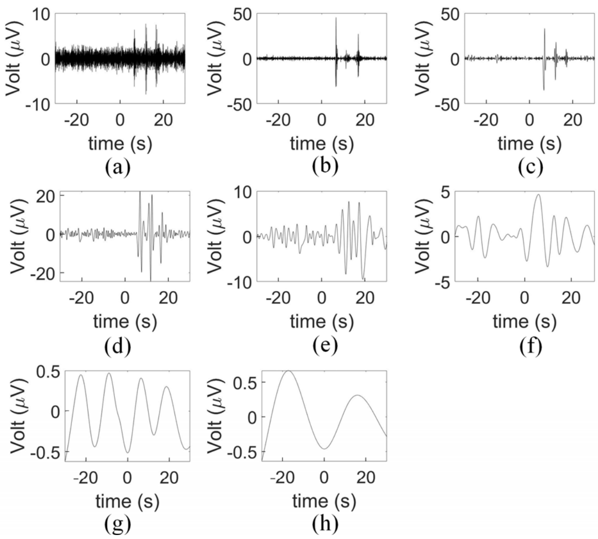

FIGURE 6. IMF extraction in a seizure event: (a) IMF-1, (b) IMF-2, (c) IMF-3, (d) IMF-4, (e) IMF-5, (f) IMF-6, (g) IMF-7, and (h) IMF-8.

nonseizure events. HRV parameters were compared between the nonseizure and seizure groups. In time-domain analysis, compared with seizure events, nonseizure events had significantly lower HR (83.4 bpm vs. 89.1 bpm, p = 0.02), higher SDNN intervals (31.3 ms vs. 29.8 ms, p = 0.01), and higher pNN50 (0.11% vs. 0.05%, p = 0.02). No significant difference was found in the RMSSD and SDSD between the groups. In frequency-domain analysis, TP, VLF, LF, HF, and LF/HF were compared. The power in each frequency band was higher for seizure events than for nonseizure events. Compared with nonseizure events, seizure events had higher HF power (734.9 ms^2 vs. 412.4 ms^2, $p < 0.01$) and LF/HF values (734.9 vs. 412.4, $p < 0.01$) (arbitrary unit).

TABLE 2. Comparison of HRV parameters between seizure and non-seizure events.

Events	NON-SEIZURE 89	SEIZURE 83	p
Variables			
Time domain			
HR	83.4 (19.8)	89.1 (10.4)	0.02
SDNN	31.3 (14.8)	29.8 (17.9)	0.01
RMSSD	45.5 (26.3)	40.1 (50.3)	0.58
SDSD	38.9 (27.8)	28.5 (28.0)	0.06
pNN50	0.11 (0.16)	0.05 (0.02)	0.02
Frequency domain			
TP	1683.8 (1861.3)	2242.1 (2954.8)	0.44
VLF	164.3 (319.3)	379.9 (319.1)	0.12
LF	125.8 (327.6)	362.4 (304.5)	0.08
HF	412.4 (101.9)	734.9 (116.7)	<0.01
LF/HF	0.3 (0.2)	0.5 (0.2)	<0.001
Nonlinear			
SampEn	0.61 (0.4)	1.24 (0.5)	<0.001
SD_1	27.6 (19.7)	20.5 (27.8)	0.06
SD_2	33.8 (29.7)	38.5 (32.8)	0.82
SD_1/SD_2	0.9 (0.3)	0.6 (0.3)	<0.001

HR = heart rate; SDNN = standard deviation of normal-to-normal beat; RMSSD = root mean square of standard deviation; SDSD = standard deviation of successive differences; pNN50 = proportion of NN50 divided by total number of NNs; TP = total power; VLF = very low frequency; LF = low frequency; HF = high frequency; LF/HF = low-to-high frequency ratio; SampEn = sample entropy; SD_1 = standard deviation of width of Poincare plot; SD_2 = standard deviation of length of Poincare plot; SD_1/SD_2 = SD_1-to-SD_2 ratio

In nonlinear analysis, parameters such as SampEn, SD_1, and SD_2, were calculated to evaluate the effect of nonlinearity. SampEn in seizure events was significantly higher than that in nonseizure events (1.24 vs. 0.61, $p < 0.001$). Figure 7 displays the Poincaré plot for nonseizure events (Figure 7(a).) and seizure events (Figure 7(b).). The average SD_1 and SD_2 values for nonseizure events were 27.6 and 33.8 ms, respectively. Moreover, the average SD_1 and SD_2 values for seizure events were 20.5 and 38.5 ms, respectively. The SD_1/SD_2 ratio for nonseizure events was significantly higher than that for seizure events (0.9 vs. 0.6, $p < 0.001$).

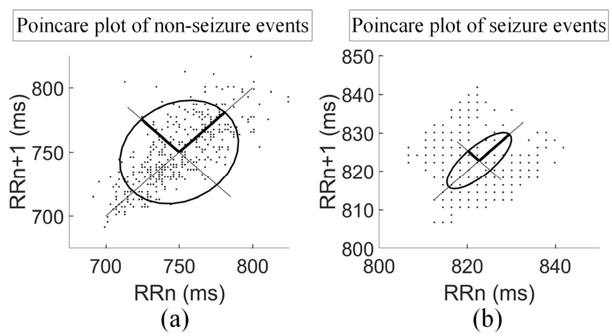

FIGURE 7. Poincaré plot for (a) nonseizure events and (b) seizure events.

Four HRV parameters, namely SDNN intervals, HF, LF/HF, and SampEn, were determined to be the optimal variables in the seizure detection model after the training algorithm and multiple logistic regression analysis were implemented. The four variables exhibited significant

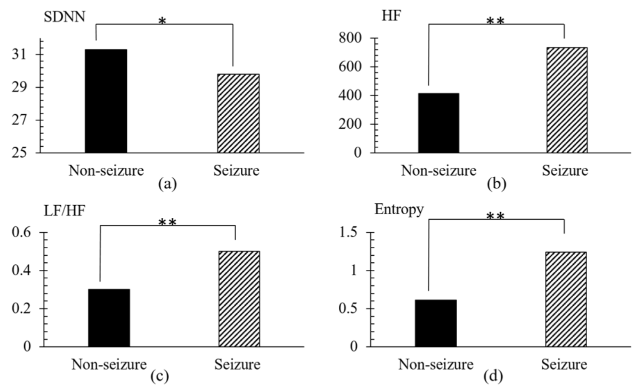

FIGURE 8. Comparison of variables in the detection model between nonseizure and seizure events.

differences between nonseizure and seizure signals, which are plotted in Figure 8(a).–(d). This model generated threshold values for assessing potential seizure events to maximize sensitivity and minimize the error. In cases where acceptable specificity was obtained for different thresholds, the threshold with the least detection error was identified. For all the 172 events, the results of the model and the assessment of the neurologist. Sensitivity was 0.74, and specificity was 0.81. The positive predictive value was 0.82.

IV. DISCUSSION

In this study, a real-time system predicting seizure events through long-term continuous data recording and extraction was developed. The system displays information on a physiological monitor and extracts real-time biosignals, including ECG and EEG signals. ECG-based HRV analysis can be used to immediately detect seizures in patients who have experienced sudden cardiac arrest and have then been resuscitated using CPR and admitted to the EICU. Four HRV parameters, namely SDNN intervals, HF, LF/HF, and SampEn, can be used to develop a reliable algorithm for seizure detection.

Seizures has always been a critical issue in clinical care scenarios, especially for patients who have survived a cardiac arrest, because the long ischemic cerebral perfusion time may cause hypoxic encephalopathy, which deteriorates neurological outcomes. The current study overcomes the previous limitations on continuity and accessibility for real-time seizure detection [13], [14]. In this study, seizure events were detected in patients presenting with muscle convulsion through physician assessments and a real-time detection model. Seizure could be also found in anytime when the patients seemed no convulsion because abnormal electrical discharge in these patients only occurred in the cerebral cortex, but not in the limbs or face. EEG signals are the most widely used type of signals for conducting analysis related to seizures. All potential seizure events, whether explicit or implicit, were recorded. The data continuity provided insights into the detection of implicit seizure events. Each recruited patient experienced more than one seizure event (14 patients, 83 seizure events). Most of these events were ignored by the physicians because the patients did not present any convulsion or abnormal physical tremors. Thus, the physicians did not note the occurrence of certain seizure events in the patients. In this scenario, the patients failed to receive antiepileptic treatment. The sensitivity and specificity obtained in the current study were lower than those obtained in Moridani's study [16]. The patients in this study had experienced OHCA, which is a disastrous physiological condition. The patients received sedative agents, which may influence the ANS activity and even suppress small seizures, which cannot be detected by EEG.

The developed system provides real-time accessibility for the detection of potential seizure events. ECG waveforms are continuously recorded and routinely used to monitor patients. The core concept of ECG is the communication between the brain and the heart. The brain directly controls the heart through the ANS, including the sympathetic and parasympathetic branches that contain multisynaptic signal routes from cardiac cells to connecting neurons. The function of the heart can be changed through the initiation of the ANS in the cardiac cells, which reflects signals from the receptors and higher-level commands [44]. The acute and chronic clinical symptoms of an imbalanced connection between the brain and the heart may have a negative effect on physical and mental health. Several ANS disorders, such as anxiety [45], depression [46], and insomnia [47], and other neurological diseases can be assessed and diagnosed through HRV analysis [48]. Theoretically, seizures that involve parts of the central autonomic network, such as the medial prefrontal cortex, insular cortex, or amygdala, suggest ANS abnormalities, such as sympathetic hyperactivity and cardiac arrhythmias [49]. The attack of seizures from the temporal lobe, particularly seizure episodes from the left hemisphere, may be correlated with high parasympathetic activity, which causes bradycardia. This phenomenon is consistent with the current findings that HF in seizure events was significantly higher than that in nonseizure events ($p < 0.001$, Figure 8(b).), and that the heart rate in seizure events was lower than that in nonseizure events (Table 2). Seizure-related cardiac arrhythmias are a potential cause of sudden unexpected death [50]. The main aim of the current study was to avoid this disaster. The balance of the ANS may be enhanced in seizure events during deep sleep or sedation that often occur before the motor response. This phenomenon may reflect the activation of ANS, called the arousal response, plays a role in seizure initiation [51]. The findings of this study indicated higher LF/HF in seizure events than in nonseizure events (Figure 8(c).).

The raw data of the current study were stored on a server for safe backup and further analysis. It provided a pragmatic and flexible seizure-data acquisition system model with minimum impact and resource cost applicable to research in critical and practical medical settings. The data continuity and real-time data accessibility could be achieved in the developed PMSDA system. The wireless network system was constructed by considering practical requirements; thus, it can be feasibly and conveniently used in emergency and critical care medicine.

Data analysis indicated that a significant difference existed between the SampEn of the seizure and nonseizure states ($p < 0.001$). In this study, the physicians administered AEDs to the patients experiencing seizures, thereby providing high-quality post-cardiac arrest care. The administration of AEDs may improve outcomes in cardiac arrest survivors.

The real-time seizure detection model exhibits the properties of continuity and accessibility. With the developed model, physicians can identify potential seizure events that were previously ignored. Thus, patients experiencing seizures can receive treatment without delay. This study has certain limitations. First, the sample size was relatively small. The research sample comprised cardiac arrest survivors admitted to only the EICU. The patients who declined further treatment and refused to sign the consent form were excluded from this study. According to the latest data, patients with ROSC account for approximately 10%–20% of the patients in hospitals, which causes difficulty in patient recruitment. Second, selection bias may exist. Cardiogenic events are the main cause of OHCA [52]. The study results indicated a relatively low rate of cardiogenic survivors (Table 1). Cardiogenic arrest may originate from acute coronary syndrome, refractory fatal arrhythmia, or heart failure. Emergency coronary angiography and extracorporeal membrane oxygenation may enhance the survival outcomes of individuals who have experienced cardiogenic arrest. Patients who have experienced cardiogenic arrest should be admitted to coronary care units rather than to EICUs for post-cardiac arrest care. In EICUs, most patients present with nonshockable initial cardiac arrest, which may imply a high rate of seizure events and low survival-to-discharge. These findings are compatible with the findings of this study. Third, biosignals are inevitably affected by environmental noise. A high SNR is a strict requirement for EEG signals. The EEG record in this study was not metallically shielded, which decreased the SNR. Although the patients in the EICU could not receive metallic shielding, other methods, such as eliminating the 60-Hz line noise, enhancing skin preparation, and optimizing the noise filter, were used to minimize the influence of the SNR. Finally, clinical manifestations such as seizures, shivering, tremors, and voluntary small movement may have similar raw signals. The findings of this study may not be applicable to other epileptic populations or the general population because the research sample only included cardiac arrest survivors. Additional studies should be conducted to obtain additional evidence for identifying the difference.

V. CONCLUSION

In this study, a robust biosignal monitoring and recording system was developed for emergency and critical care. HRV analysis indicated potential ANS disorders, which enabled the real-time detection of seizure events in cardiac arrest survivors. Parameters such as SDNN intervals, HF, LF/HF, and SampEn are important factors for predicting seizures. Additional studies should be conducted to extend the findings of this study to different clinical scenarios.

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REFERENCES

[1] A. S. Go, A. S. Go, D. Mozaffarian, and V. L. Roger, "Heart disease and stroke statistics–2014 update: A report from the American heart association," *Circulation*, vol. 129, no. 3, pp. e28–e292, Jan. 21, 2014.

[2] J. Berdowski, R. A. Berg, J. G. P. Tijssen, and R. W. Koster, "Global incidences of out-of-hospital cardiac arrest and survival rates: Systematic review of 67 prospective studies," *Resuscitation*, vol. 81, no. 11, pp. 1479–1487, Nov. 2010.

[3] I. Hasselqvist-Ax, G. Riva, and J. Herlitz, "Early cardiopulmonary resuscitation in out-of-hospital cardiac arrest," *New England J. Med.*, vol. 372, no. 24, pp. 2307–2315, Jun. 11, 2015.

[4] S. P. Keenan, "Variation in length of intensive care unit stay after cardiac arrest: Where you are is as important as who you are," *Crit. Care Med.*, vol. 35, no. 3, pp. 836–841, Mar. 2007.

[5] J. P. Nolan, "Outcome following admission to UK intensive care units after cardiac arrest: A secondary analysis of the ICNARC Case Mix Programme Database," *Anaesthesia*, vol. 62, no. 12, pp. 1207–1216, Dec. 2007.

[6] K. Mashiko, "An outcome study of out-of-hospital cardiac arrest using the Utstein template—A Japanese experience," *Resuscitation*, vol. 55, no. 3, pp. 241–246, Dec. 2002.

[7] S. Laver, C. Farrow, D. Turner, and J. Nolan, "Mode of death after admission to an intensive care unit following cardiac arrest," *Intensive Care Med.*, vol. 30, no. 11, pp. 2126–2128, Nov. 2004.

[8] P. Vaagenes, "Cerebral resuscitation from cardiac arrest: Pathophysiologic mechanisms," *Crit. Care Med.*, vol. 24, no. 2, pp. 57–68, Feb. 1996.

[9] A. R. Towne, E. J. Waterhouse, J. G. Boggs, and L. K. Garnett, "Prevalence of nonconvulsive status epilepticus in comatose patients," *Neurology*, vol. 54, no. 2, pp. 340–345, Jan. 2000.

[10] E. C. Stecker, "Relationship between seizure episode and sudden cardiac arrest in patients with epilepsy: A community-based study," *Circulat., Arrhythmia Electrophysiol.*, vol. 6, no. 5, pp. 912–916, Oct. 2013.

[11] A. Van de Vel, "Non-EEG seizure-detection systems and potential SUDEP prevention: State of the art," *Seizure*, vol. 22, no. 5, pp. 345–355, Jun. 2013.

[12] B. Litt, R. Esteller, J. Echauz, M. D'Alessandro, and R. Shor, "Epileptic seizures may begin hours in advance of clinical onset: A report of five patients," *Neuron*, vol. 30, no. 1, pp. 51–64, Apr. 2001.

[13] K. Fujiwara, "Epileptic seizure prediction based on multivariate statistical process control of heart rate variability features," *IEEE Trans. Biomed. Eng.*, vol. 63, no. 6, pp. 1321–1332, Jun. 2016.

[14] K. Fujiwara, E. Abe, K. Kamata, C. Nakayama, Y. Suzuki, T. Yamakawa, T. Hiraoka, M. Kano, Y. Sumi, F. Masuda, M. Matsuo, and H. Kadotani, "Heart rate variability-based driver drowsiness detection and its validation with EEG," *IEEE Trans. Biomed. Eng.*, vol. 66, no. 6, pp. 1769–1778, Jun. 2019.

[15] P.-F. Lin, M.-T. Lo, J. Tsao, Y.-C. Chang, C. Lin, and Y.-L. Ho, "Correlations between the signal complexity of cerebral and cardiac electrical activity: A multiscale entropy analysis," *PLoS ONE*, vol. 9, no. 2, Feb. 2014, Art. no. e87798.

[16] M. K. Moridani and H. Farhadi, "Heart rate variability as a biomarker for epilepsy seizure prediction," *Bratislava Med. J.*, vol. 118, no. 1, pp. 3–8, 2017.

[17] J. Jeppesen, A. Fuglsang-Frederiksen, and P. Johansen, "Seizure detection using heart rate variability: A prospective validation study," *Epilepsia*, to be published.

[18] J. Jeppesen, A. Fuglsang-Frederiksen, P. Johansen, J. Christensen, S. Wüstenhagen, H. Tankisi, E. Qerama, A. Hess, and S. Beniczky, "Seizure detection based on heart rate variability using a wearable electrocardiography device," *Epilepsia*, vol. 60, no. 10, pp. 2105–2113, Oct. 2019.

[19] G. Giannakakis, M. Tsiknakis, and P. Vorgia, "Focal epileptic seizures anticipation based on patterns of heart rate variability parameters," *Comput. Methods Programs Biomed.*, vol. 178, pp. 123–133, Sep. 2019.

[20] L. Billeci, D. Marino, L. Insana, G. Vatti, and M. Varanini, "Patient-specific seizure prediction based on heart rate variability and recurrence quantification analysis," *PLoS ONE*, vol. 13, no. 9, Sep. 2018, Art. no. e0204339.

[21] S. Behbahani, "A review of significant research on epileptic seizure detection and prediction using heart rate variability," *Turk Kardiyoloji Dernegi Arsivi-Arch. Turkish Soc. Cardiol.*, pp. 414–421, 2018.
[22] J. Jeppesen, S. Beniczky, A. Fuglsang-Frederiksen, P. Sidenius, and Y. Jasemian, "Detection of epileptic-seizures by means of power spectrum analysis of heart rate variability: A pilot study," *Technol. Health Care*, vol. 18, no. 6, pp. 417–426, Nov. 2010.
[23] S. Behbahani, N. J. Dabanloo, A. M. Nasrabadi, C. A. Teixeira, and A. Dourado, "Pre-ictal heart rate variability assessment of epileptic seizures by means of linear and non-linear analyses," *Anadolu Kardiyoloji Dergisi/Anatolian J. Cardiol.*, pp. 797–803, Oct. 2013.
[24] D. Bzdok, N. Altman, and M. Krzywinski, "Statistics versus machine learning," *Nature Methods*, vol. 15, no. 4, pp. 233–234, Apr. 2018.
[25] G. G. Berntson, J. T. Bigger, Jr., D. L. Eckberg, P. Grossman, P. G. Kaufmann, M. Malik, and H. N. Nagaraja, "Heart rate variability: Origins, methods, and interpretive caveats," *Psychophysiology*, vol. 34, no. 6, pp. 623–648, Nov. 1997.
[26] M. Malik, "Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. task force of the European society of cardiology and the North American society of pacing and electrophysiology," *Eur. Heart J.*, vol. 17, no. 3, pp. 354–381, Mar. 1996.
[27] J. J. Żebrowski, I. Kowalik, E. Orłowska-Baranowska, M. Andrzejewska, R. Baranowski, and J. Gierałtowski, "On the risk of aortic valve replacement surgery assessed by heart rate variability parameters," *Physiol. Meas.*, vol. 36, no. 1, pp. 163–175, Jan. 2015.
[28] L. Claudia, I. Oscar, P.-G. Hector, and V. J. Marco, "Poincare plot indexes of heart rate variability capture dynamic adaptations after haemodialysis in chronic renal failure patients," *Clin. Physiol. Funct. Imag.*, vol. 23, no. 2, pp. 72–80, Mar. 2003.
[29] E. Toledo, O. Gurevitz, H. Hod, M. Eldar, and S. Akselrod, "Wavelet analysis of instantaneous heart rate: A study of autonomic control during thrombolysis," *Amer. J. Physiol.-Regulatory, Integrative Comparative Physiol.*, vol. 284, no. 4, pp. R1079–R1091, Apr. 2003.
[30] P. Guzik, J. Piskorski, T. Krauze, and R. Schneider, "Correlations between Poincaré plot and conventional heart rate variability parameters assessed during paced breathing," *J. Physiol. Sci.*, vol. 57, no. 1, pp. 63–71, Feb. 2007.
[31] S. M. Pincus, I. M. Gladstone, and R. A. Ehrenkranz, "A regularity statistic for medical data analysis," *J. Clin. Monit.*, vol. 7, no. 4, pp. 335–345, Oct. 1991.
[32] M. Sabeti, S. Katebi, and R. Boostani, "Entropy and complexity measures for EEG signal classification of schizophrenic and control participants," *Artif. Intell. Med.*, vol. 47, no. 3, pp. 263–274, Nov. 2009.
[33] A. Zeiler, R. Faltermeier, I. Keck, A. Tomé, C. Puntonet, and E. W. Lang, "Empirical mode decomposition-an introduction," in *Proc. Int. Joint Conf. Neural Netw. (IJCNN)*, Jul. 2010, pp. 1–8.
[34] N. E. Huang, Z. Shen, S. R. Long, M. C. Wu, H. H. Shih, Q. Zheng, N.-C. Yen, C. C. Tung, and H. H. Liu, "The empirical mode decomposition and the Hilbert spectrum for nonlinear and non-stationary time series analysis," *Proc. Roy. Soc. London. A, Math., Phys. Eng. Sci.*, vol. 454, no. 1971, pp. 903–995, Mar. 1998.
[35] J. Ramakrishnan and B. R. Kanagaraj, "Analysis of non-seizure and seizure activity using intracranial EEG signals and empirical mode decomposition based approximate entropy," *Biomed. Res.*, to be published.
[36] N. A. Al-Thanoon, O. S. Qasim, and Z. Y. Algamal, "Tuning parameter estimation in SCAD-support vector machine using firefly algorithm with application in gene selection and cancer classification," *Comput. Biol. Med.*, vol. 103, pp. 262–268, Dec. 2018.
[37] T. Netoff, Y. Park, and K. Parhi, "Seizure prediction using cost-sensitive support vector machine," in *Proc. Annu. Int. Conf. IEEE Eng. Med. Biol. Soc.*, Sep. 2009, pp. 3322–3325.
[38] G. Li and W. Y. Chung, "Detection of driver drowsiness using wavelet analysis of heart rate variability and a support vector machine classifier," *Sensors*, vol. 13, no. 12, pp. 16494–16511, Dec. 2013.
[39] N. Acir, I. Oztura, M. Kuntalp, B. Baklan, and C. Guzelis, "Automatic detection of epileptiform events in EEG by a three-stage procedure based on artificial neural networks," *IEEE Trans. Biomed. Eng.*, vol. 52, no. 1, pp. 30–40, Jan. 2005.
[40] Y. Liu, W. Zhou, Q. Yuan, and S. Chen, "Automatic seizure detection using wavelet transform and SVM in long-term intracranial EEG," *IEEE Trans. Neural Syst. Rehabil. Eng.*, vol. 20, no. 6, pp. 749–755, Nov. 2012.
[41] G. C. Cawley and N. L. C. Talbot, "Fast exact leave-one-out cross-validation of sparse least-squares support vector machines," *Neural Netw.*, vol. 17, no. 10, pp. 1467–1475, Dec. 2004.
[42] K. Ajam, L. S. Gold, S. S. Beck, S. Damon, R. Phelps, and T. D. Rea, "Reliability of the cerebral performance category to classify neurological status among survivors of ventricular fibrillation arrest: A cohort study," *Scandin. J. Trauma, Resuscitation Emergency Med.*, vol. 19, no. 1, p. 38, 2011.
[43] S. S. Shapiro and M. Wilk, "An analysis of variance test for normality (complete samples)," *Biometrika*, vol. 52, no. 3, pp. 591–611, Dec. 1965.
[44] A. Silvani, G. Calandra-Buonaura, R. A. Dampney, and P. Cortelli, "Brain–heart interactions: Physiology and clinical implications," *Philos. Trans. Roy. Soc. A, Math., Phys. Eng. Sci.*, vol. 374, no. 2067, May 2016, Art. no. 20150181.
[45] K. H. Liao, C. W. Sung, S. F. Chu, W. T. Chiu, and Y. H. Chiang, "Reduced power spectra of heart rate variability are correlated with anxiety in patients with mild traumatic brain injury," *Psychiatry Res.*, vol. 243, pp. 349–356, Sep. 2016.
[46] C. W. Sung, H. C. Lee, Y. H. Chiang, and W. T. Chiu, "Early dysautonomia detected by heart rate variability predicts late depression in female patients following mild traumatic brain injury," *Psychophysiology*, vol. 53, no. 4, pp. 455–464, Apr. 2016.
[47] C.-N. Ho, P.-H. Fu, J.-Y. Chen, K.-C. Hung, J.-H. Chang, C.-K. Peng, and A. C. Yang, "Heart rate variability and surgical pleth index under anesthesia in poor and normal sleepers," *J. Clin. Monitor. Comput.*, to be published.
[48] V. P. da Silva, B. R. Ramalho Oliveira, R. G. Tavares Mello, H. Moraes, A. C. Deslandes, and J. Laks, "Heart rate variability indexes in dementia: A systematic review with a quantitative analysis," *Current Alzheimer Res.*, vol. 15, no. 1, pp. 80–88, Dec. 2017.
[49] C. Richard, "Stress-related cardiomyopathies," *Ann. Intensive Care*, vol. 1, no. 1, p. 39, Sep. 2011.
[50] P. Tinuper, F. Bisulli, A. Cerullo, R. Carcangiu, and C. Marini, "Ictal bradycardia in partial epileptic seizures: Autonomic investigation in three cases and literature review," *Brain*, vol. 124, no. 12, pp. 2361–2371, Dec. 2001.
[51] G. Calandra-Buonaura, N. Toschi, F. Provini, and I. Corazza, "Physiologic autonomic arousal heralds motor manifestations of seizures in nocturnal frontal lobe epilepsy: Implications for pathophysiology," *Sleep Med.*, vol. 13, no. 3, pp. 252–262, Mar. 2012.
[52] A. Myat, K.-J. Song, and T. Rea, "Out-of-hospital cardiac arrest: Current concepts," *Lancet*, vol. 391, no. 10124, pp. 970–979, Mar. 2018.

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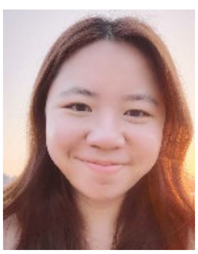

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