Predicting intensive care outcomes in traumatic brain injury using heart rate variability measures with feature extraction strategies

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***Abstract*— Prediction of patient outcome in medical intensive care units (ICU) may help for development of early interventional strategies. Several ICU scoring systems have been developed and are used to predict clinical deterioration of ICU patients. These scores are calculated from characteristics of patients and clinical records. Heart rate variability (HRV) is a correlate of cardiac autonomic regulation and has been evident as a marker in many critical diseases. It can be measured based on electrocardiogram (ECG) which is non-invasive and can be real time monitored. HRV has been identified as a promising 'electronic biomarker' of disease severity. Traumatic brain injury (TBI) is a subset of critically ill patients, admitted to ICU. Changes of HRV for brain injured patients have been reported in several studies. This study aimed to utilize the continuous HRV collection from admission for the first 24 hours in the ICU in severe TBI patients, and develop a patient outcome prediction system. A feature extraction strategy was applied to measure the HRV fluctuation during time. A prediction model was developed based on HRV measures collected for the first day of patient admission to the ICU. The result was compared with current evaluated ones, and showed promising result for further development and potential for practical application.**

Keywords*— *ECG, time series, HRV, feature extraction, Euclidean distance, patient outcome, ICU

I. Background

The development of a prediction model, based on the continuous monitoring of physiological signals to predict clinical outcome, may allow for early identification of deterioration and ultimately guide interventional strategies which may improve survivability rates, or in cases of poor outcome, inform end-of-life decisions. Currently there are several ICU scoring systems in place to measure the severity of disease within 24 hours of a patient admission to ICU, including the Acute Physiology and Chronic Health Evaluation (APACH II and the updated versions APACHE III/IV) [1, 2, 3, 4], Simplified Acute Physiology Score (SAPS II) [5], Multiple Organ Dysfunction Score (MODS) [6] and the Sequential Organ Failure Assessment (SOFA) etc [7, 8]. These scores correspond to the risk of death, and are used for prediction of mortality of patients in various diseases. They are calculated based on characteristics of patients including age, chronic health, major medical and surgical disease categories, acute physiologic abnormalities, pre-existing functional limitations, major comorbidities, and ICU admission variables (including patient location before ICU, drug overdose etc), with slightly difference of variables used in each scoring system. Strong correlation between these scores may exist [8, 9]. Predictive ability of these scoring systems on ICU patient outcome have been evaluated by researchers across the world [10, 11], and reportedly APACHE and SAPS are highly advanced and prospectively verified [12, 13]. None the less, these scores do not take into account heterogeneity between patients from minutely changing physiological variability.

II. Heart rate variability and traumatic brain injury

The Electrocardiogram (ECG) is a non-invasive measure of the heart's overall electrical activity and is measured continuously during a patient's stay in the ICU. ECG waveform interpretation has provided the basis for clinical diagnosis of progressive heart disease and lethal arrhythmias. A novel extension of ECG monitoring is assessing the beat-to-beat variation in heart rate (HR) termed Heart Rate Variability (HRV). In a healthy individual, autonomic nervous system (ANS) activity is a key regulator of HR; changes in parasympathetic and sympathetic nervous system during normal circadian rhythm lead to HR fluctuations. HRV is a correlate of cardiac autonomic regulation and has been identified as a promising 'electronic biomarker' of disease severity and predicting patient outcomes. The Chinese physician, Wang SU Ho (256-317 A.D), noted the variability of the heart as an indicator of the critically ill: "If the pattern of the heart beat becomes as regular as the tapping of a woodpecker or the dripping of rain from the roof, the patient will be dead in 4 days" [14].

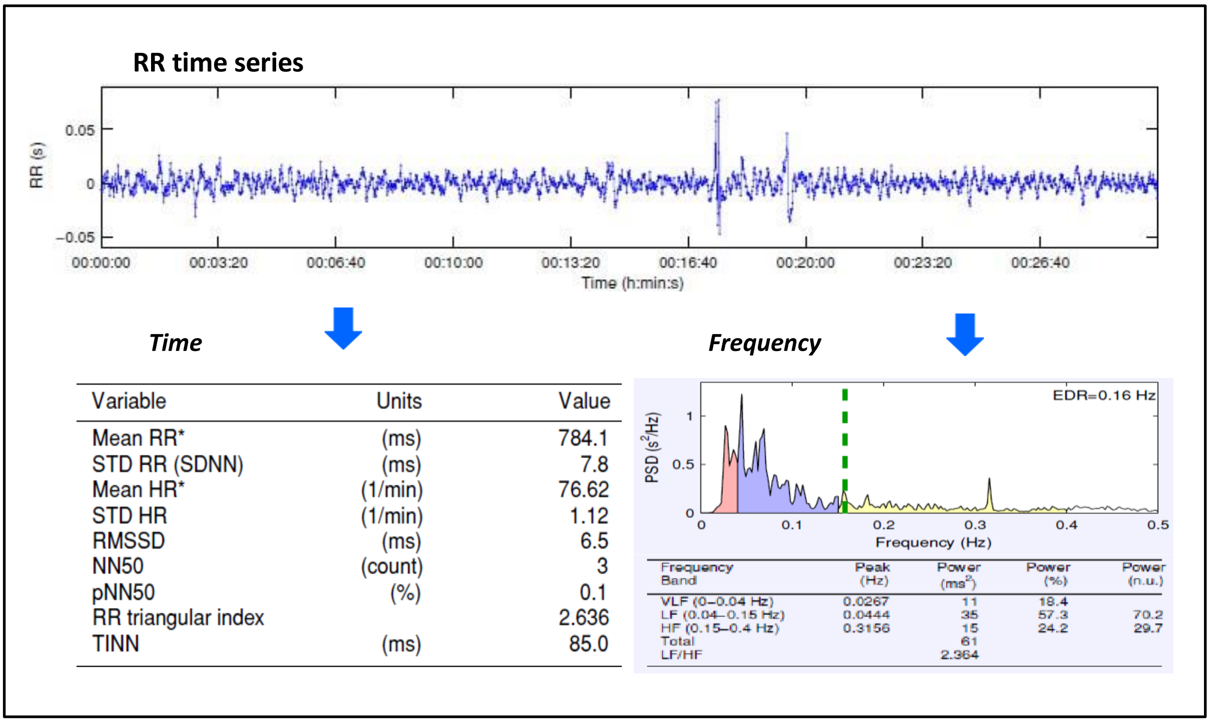
HRV is the variation in time between consecutive heart beats (RR interval) and can be analysed in both time and frequency domains. Time domain analysis calculates and assess the overall RR interval time series and frequency domain analysis quantifies the overall variability as frequency of ANS function.

HRV analysis in time domain is the simplest quantification method of HRV, calculated on a beat-to-beat basis. In the literature, RR intervals of normal sinus rhythm are denoted as normal-to-normal (NN) beats. Standard deviation of the NN interval (SDNN) reflects all the cyclic components responsible for variability within the recording time period, for example a 24-hour period. The square root of the mean square differences of successive NN intervals (RMSSD) reflects high frequency variations in heart rate. RMSSD is highly correlated with both NN50, the number of successive NN beats that differ by more than 50ms and pNN50 the percentage of NN50 over the entire NN series. The statistical properties of RMSDD are preferred to pNN50 and NN50 (Figure 1). Whilst time domain methods can be calculated from short 5min signals to entire 24-hour signals, it is recommended that comparisons between different recording lengths in the time domain be avoided as HRV is not a stationary process.

Frequency domain measurements estimate the distribution of absolute or relative signal energy into four frequency bands. Frequency Domain Analysis shows how much of a signal lies within one or more frequency bands (ranges). The Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (1996) divided HR oscillations into ultra-low-frequency (ULF), very-low-frequency (VLF), low-frequency (LF), and high-frequency (HF) bands. The power (Figure 1) within these frequency ranges represents the overall variance, expressed as milliseconds squared (ms^2), implying the greater the power, the greater variation. Total Power (TP) is a measure of overall variance in RR intervals accounting for all sources, nervous, hormonal and circadian. It is a measure of overall variation in HR – the greater the TP the more variance there is within the time series, therefore the heart can adapt quicker to stimulus. LF and HF may also be measured as normalised (nu) (LFnu, HFnu) representing the relative value of each power whilst correcting for TP. This makes comparison between individuals as it accounts for their individual variance. More details about on HRV measures in both time and frequency domains can be found in reference [15].

Traumatic brain injury (TBI) is one of the leading causes of death and disability worldwide, with TBI accounting for up to 50% of patients admitted to the intensive care unit (ICU). The latest annual incidence of TBI worldwide indicated that incidence is currently 295/100,000 for all ages [16]. By 2030, brain injuries due to traffic accidentals are expected to rise to the 7th leading cause of death [17]. Treatment of TBI is confounded by the wide heterogeneity between patient presentations, extensive comorbidities and the widespread secondary complications that evolve from the primary damage. This diversity between patients makes injury severity difficult to gauge, thus clinicians are always looking for newer, patient specific indicators of secondary brain injury evolution and possible complications. A method of predicting patient outcome, such as that described here, that may assist in clinical decisions and allows for more informed discussions in family meetings would be a useful tool that could be incorporated into the ICU workflow.

Autonomic impairment after acute TBI has been associated independently with increased morbidity and mortality [18] [19], thus HRV, as a correlate of ANS regulation of HR, provides an ideal physiological marker to form the basis of a prediction model. Changes in HRV for brain injured patients have been reported in several studies [20, 21, 22, 23, 24, 25]. In these studies, both time and frequency domains of ECG signals were analysed. Winchell et al [26] studied the effect of alterations in HRV on mortality in a surgical ICU population, and reported that low TP (low



Variable	Units	Value
Mean RR*	(ms)	784.1
STD RR (SDNN)	(ms)	7.8
Mean HR*	(1/min)	76.62
STD HR	(1/min)	1.12
RMSSD	(ms)	6.5
NN50	(count)	3
pNN50	(%)	0.1
RR triangular index		2.636
TINN	(ms)	85.0

Frequency Band	Peak (Hz)	Power (ms^2)	Power (%)	Power (n.u.)
VLF (0–0.04 Hz)	0.0267	11	18.4	
LF (0.04–0.15 Hz)	0.0444	35	57.3	70.2
HF (0.15–0.4 Hz)	0.3156	15	24.2	29.7
Total		61		
LF/HF		2.364		

Fig 1: Example of RR time series analysis in the Time and Frequency domains. The RR time series are derived into the time and frequency domains. Time domain calculates overall variability within the sample' frequency domain calculates autonomic modulation.

autonomic tone) and high HF/LF ratio (relative lack of sympathetic tone) were associated with increased mortality. A low HF/LF ratio (relatively high sympathetic tone) was also found to be associated with increased survival, especially in patients with low autonomic tone. Sykora et al. [20] reported that over long term-indiscriminate averaging, autonomic impairment associated with increased HF powers and decreased LH/HF ratio, as measured by HRV, is significantly associated with increased mortality after TBI, independent of ICP and CPP. For every increase in relative HR power, the odds for mortality increased by 4.6%. Haji-Michael et al [27] showed that brain injured patients had reduced HRV, such as a lowered total power variability of RR and a lowered LF/HF ratio of the RR, whereas recovery of HRV was associated with an improved outcome. Kox et al [28] also investigated the association of HRV in brain injury patients with innate immune system. They found that higher levels of HFnu were correlated with attenuated levels of plasma Tumour Necrosis Factor Alpha (TNF-α), implicating reduction in inflammatory mediators and thus demonstrating an immune-suppressive mechanism of action. In the subgroup of patients with intracranial haemorrhage (ICH), there were higher intracranial pressure (ICP) that were correlated to an even higher degree of HFnu and immune suppression. Association of brain death with HRV was reported in the study of Baillard et al [29]. Piantino et al [30] also reported that children who progressed to brain death exhibited lower HRV in both time and frequency domains. These findings suggest ANS dysfunction may be implicated with poor outcomes and indicate that HRV may be a promising predictor of adverse outcomes in TBI patients.

The analyses of the above studies were based on univariate analysis. In addition, most research regarding TBI and HRV was only carried out with periodic calculations (5min or 10min recordings), within the acute phase of brain injury (72 hours post ictus) and free of interventions and confounding medication. This study aims to investigate the aspects of continuous HRV collection from admission across the first 24 hr of stay in the ICU in severe TBI patients, and utilize the continuous HRV measurement to develop a patient outcome prediction system. The advantages of using HRV analysis is that it utilises cardiovascular biosignals that are readily available, pre-existing standards of care, patient specific and inexpensive, which means that earlier identification outcome in these patient group may be improved without an increase in cost of care.

III. METHODOLOGY

The goal of this study was to utilize the 24 hours continuous HRV measurement and develop a surviving prediction system applied to ICU TBI patients. For this study, the model development can be described as 3 parts: data collection, feature extraction and building of prediction models. See figure 2.

A. *Data collection*

Electrocardiogram (ECG), mechanical ventilation parameters, medication and the Glasgow Coma Scale (GCS) are standards of care that are continuously monitored throughout a patient's Intensive Care Unit (ICU) stay. For this study, 26 ICU patients with diagnosed TBI were sampled [31]. Medical records and 24 hours ECG data were collected from the patient bedside GE monitor via a separate output at 300hz. Twenty one of these patients survived ICU admission to be discharged to the ward without complications; five patients did not survive ICU (non-survivors). Age, gender, etiology of injury and diagnosis were also recorded upon admission to the ICU.

B. *Feature extraction*

Based on the patient medical records, APAHE II [2], APACH III [3], and SAPS II [5] scores were calculated for each patient. The 24-hour ECG signals were analysed using Kubios HRV software [32] (version 2.2), and HRV parameters were calculated over consecutive 30-minute epochs in both the time and frequency domains. The parameters calculated based on time domain included: SDNN, RMSSD and CVRR (the coefficient of variation of R-R intervals). Frequency analysis included LF, HF and LF/HF ratio, representing sympathetic, parasympathetic and sympathovagal balance respectively. Normalised units, LFnu and HFnu are calculated taking into account TP.

To utilize the consecutive HRV parameters calculated on both time domain and frequency domain, Euclidean distance between a time series and a uniformed distribution was used to measure the variance of the calculated HRV parameters during the consecutive time periods. For example, for a n consecutive 30-minutes ECG signal, there are number of n SDNN calculated. To measure the fluctuation of SDNN across the n consecutive epochs, a Euclidean distance between the vector of n values of SDNN and a baseline with a vector of n zeros is calculated as a feature of the corresponding time point of the patient. For patient i, a Euclidean distance feature can be calculated with the formula below:

$$\mathrm{DistF}_{i\_nseg}=\sqrt{F_{i1}^2+F_{i2}^2+\cdots\ldots F_{in}^2} \qquad i=1,2,\ldots\ldots M$$

M is total number of the patients, F is a feature to be calculated, for example SDNN. For this study, a total number of 20 HRV parameters calculated from Kubios were extracted (Table I) and 20 Euclidean distance features based on these parameters were calculated for each patient.

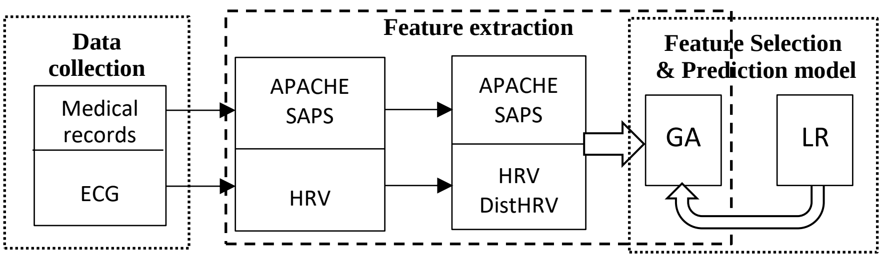


Fig 2: A diagram of proposed method

Due to the nature of the data we collected, which included 2 patients that did not survive for more than 12 hours from admission, for this study a length of 8 consecutive time points were used for calculating the Euclidean distance features (DistF). For each patient at each time point (a 30 minutes time period) the corresponding DistF was calculated based on the following 8 time points (inclusive).

For example, for a patient with 24 hours ECG data collected there would be HRV data collected at 48 time points during each 30 minutes. Therefore, there will be 41 DistF calculated corresponding to 41 time points, which can be used for building the prediction model. The data structure for this patient would be like that is shown in Table II. Prediction models will be built with the sets of selected features from the whole set.

TABLE I. LIST OF HRV PARAMETERS/FEATURES EXTRACTED FROM ECG SIGNALS

HRV Parameter	Description (30 minutes ECG)
HR	The mean heart rate
RR	The mean of RR intervals
SDNN	Standard deviation of RR intervals
RMSSD	Square root of the mean squared differences between successive RR intervals
CVRR	Coefficient of variation of R-R intervals
VLF_HZ	Peak frequency for VLF band
LF_HZ	Peak frequency for LF band
HF_HZ	Peak frequency for HF band
VLF_ms_sq	Absolute power of VLF band
LF_ms_sq	Absolute power of LF band
HF_ms_sq	Absolute power of HF band
VLF_perc	Relative powers of VLF band
LF_perc	Relative powers of LF band
HF_perc	Relative powers of HF band
LF_nu	Power of LF band in normalized unit
HF_nu	Power of HF band in normalized unit
Total_ms_sq	Total spectral power
LF/HF	Ratio between LF and HF band powers
SD1	Standard deviation of Poincaré plot, nonlinear method to measure short-term variability
SD2	Standard deviation of Poincaré plot, nonlinear method to measure long-term variability

Prediction models

In all the found literature, logistic regression (LR) equations were used for the transformation of the (severity) score into a probability of death in hospitals. To compare the predictability of HRV parameters with that of APACHE scores, LR was used as a classification method in this research. To search the best set of HRV features for predicting the probability of individual mortality, a genetic algorithm was applied for this study.

A genetic algorithm (GA) is a search heuristic to find optimal solutions for a problem. In this study, it is used for selecting the best feature set for a classification/prediction model, which is here built with logistic regression method. The best feature sets were defined as the ones that discriminate the best between survivors and non-survivors. The discrimination can be measured by false positive rate and false negative rate of the classification. A ROC curve [33] measurement, for example the area under the curve (AUC), can also be used for choosing the best model for its overall performance. For this study, a Youden's index [34] was used as the fitness function, considering that AUC does not measure a specific prediction accuracy which is needed in practice. More details about how to implement the GA with logistic regression can be found in reference [35, 36, 37].

Separate prediction models using APACHE II, APACHE III and SAPS scores will be built for comparison.

IV. EXPERIMENTAL RESULTS

The experiments were designed to apply GA with LR using 1) 20 HRV features only, and 2) HRV features and HRV based Euclidean distance features (40 in total). The results are then compared with the LR using APACHE II, APACHE III, SAPS or the combinations of them.

All the experimental results presented in the section were from the runs with 5 repeated 5-fold cross validation, with the same dataset splits applied to all the compared models. The final sets of features selected by GA were based on 100 repeated Runs. For each 5-fold cross validation, the testing set included 1 non-survivor and 20% (4) of the survived patients with 5 time points (and the following 8 time points) randomly selected for each patient (total of 5*5=25 data points). The rest of the whole dataset was used to train the models. A Youden's

TABLE II. DATA STRUCTURE FOR ONE PATIENT

Time point (Time period)	HRV features				HRV Euclidean distance features				
	HR	RR	......	SD2	Time points for calculation	DistHR	DistRR	......	DistSD2
1[0,30min)*	57.7	1040.7	......	8.5	1-8	166.9	2884.1	......	32.6
2[30,60min)	56.3	1066.0	......	12.4	2-9	167.3	2876.5	......	33.4
⋮	⋮	⋮	......	⋮	⋮	⋮	⋮	......	⋮
40 [23,23.5hr)*	40.0	957.8	......	15.1	40-47	259.3	2019.8	......	40.2
41 [23.5,24hr)	68.5	877.1	......	12.0	41-48	272.3	......	......	39.0

*[0, 30min) represent the first 30minutes of the ECG record. [23,23.5hr) represents from the 23rd hour to 23.5 hour ECG record.

index value from the 5 fold cross validated testing result was used as the fitness function of GA. Table III shows the results from the different feature sets, with the AUC, sensitivity and specificity from the final model reported. Feature set 6 (LF_hz, HF_hz, LF_perc and LFHF) were selected from the whole set of 20 original HRV features by GA. Feature set 7 and 8 were the subset selected from the total number of 40 HRV features and HRV based DistF. We can see with the probability cut off 0.5 from the LR model, all the models produced higher specificity than the sensitivity. The models with APACH III included as a variable/feature basically could not predict any non-survivors correctly with the default probability cut off 0.5. Overall, the HRV based features worked better than the previously adopted injury severity scores. The models created with these selected features produced higher AUC, and higher sensitivity with similar specificity. Of the previously adopted illness severity scores, only APACH II gave a reasonably competitive result.

V. Conclusion

The novelty of this study is utilizing feature extraction strategies to predict outcome of ICU patients with only HRV parameters derived from the ECG. The comparison between the prediction models built with different feature sets indicated that HRV based parameters alone may predict the brain injury patient outcome better than the previously adopted illness severity scores. The Euclidean distance features extracted based on the basic HRV parameters contributed to the prediction models significantly. The limitation of this study is that there were only 5 non-survivors in the data collected, and 2 of them did not survive until the data collection was completed. With this limitation, our Euclidean distance features were calculated with eight 30-min consecutive HRV measurement. This can be expanded to a longer time period in our future studies. Based on these findings, we are encouraged to test the method on a larger patient cohort , to develop a practical model that is able to predict ICU brain injury patient outcome based solely on ECG derived HRV parameters.

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TABLE III. CROSS VALIDATION RESULTS FROM THE MODELS BUILT WITH DIFFERENT

		Training			Testing		
Set #	**Features**	**AUC [95% CI]**	**Sensitivity**	**Specificity**	**AUC**	**Sensitivity**	**Specificity**
1	APACHE II	0.73 [0.7, 0.76]	0.23 [0.15, 0.31]	1 [1, 1]	0.74 [0.63, 0.84]	0.16 [0.01, 0.31]	1 [1, 1]
2	APACHE III	0.6 [0.56, 0.64]	0.07 [0.01, 0.13]	1 [0.99, 1]	0.59 [0.43, 0.75]	0 [0, 0]	0.98 [0.95, 1.01]
3	SAPS	0.73 [0.7, 0.75]	0.08 [0.02, 0.14]	0.96 [0.95, 0.98]	0.74 [0.65, 0.84]	0.04 [0, 0.12]	0.95 [0.91, 0.99]
4	APACHE II APACHE III	0.77 [0.74, 0.79]	0.2 [0.12, 0.28]	0.96 [0.95, 0.98]	0.65 [0.55, 0.75]	0 [0, 0]	0.96 [0.92, 1]
5	APACHE II APACHE III SAPS	0.78 [0.76, 0.81]	0.23 [0.15, 0.31]	0.96 [0.95, 0.98]	0.64 [0.53, 0.75]	0 [0, 0]	0.9 [0.84, 0.96]
6	LF_hz HF_hz LF_perc LFHF	0.8 [0.77, 0.83]	0.35 [0.26, 0.44]	0.97 [0.97, 0.98]	0.75 [0.66,0.84]	0.22 [0.08,0.35]	0.93 [0.89,0.97]
7	DistHR DistHF_hz DistHF_perc DistLFHF	0.87 [0.85, 0.9]	0.6 [0.54, 0.66]	0.96 [0.95, 0.96]	0.76 [0.64, 0.88]	0.52 [0.34, 0.7]	0.93 [0.9, 0.97]
8	HR DistHR DistHF_hz DistVLF_perc DistHF_perc DistLFHF	0.9 [0.87, 0.92]	0.68 [0.62, 0.73]	0.96 [0.96, 0.97]	0.77 [0.66, 0.89]	0.65 [0.48, 0.82]	0.92 [0.88, 0.96]
9	HR DistHR DistHF_hz DistLFHF	0.86 [0.83, 0.88]	0.62 [0.56, 0.69]	0.95 [0.94, 0.96]	0.76 [0.64, 0.88]	0.5 [0.31, 0.68]	0.93 [0.89, 0.97]

*Sensitivity and specificity were calculated with a probability of 0.5 from LR as a cut-off, which means when the output from LR is over than 0.5, it was classified as positive, otherwise negative.

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