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RESEARCH ARTICLE

Mortality Prediction of ICU Cardiovascular Patient: Time-Series Analysis

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Abstract

It is estimated that millions of deaths occur annually, which can be prevented when early diagnosis and correct treatment are provided in the intensive care unit (ICU). In addition to monitoring and treating patients, the physician of the ICU has the task of predicting the outcome of patients and identifying them. They are also responsible for the separation of patients who use special ICUs. Because not necessarily all patients hospitalized in ICU benefit from this unit, and hospitalization in a few cases will only lead to an easier death. Therefore, developing an intelligent method that can help doctors predict the condition of patients in the ICU is very useful. This paper aims to predict the mortality of cardiovascular patients hospitalized in the ICU using cardiac signals. In the proposed method, the condition of patients is predicted 30 minutes before death using various features extracted from the electrocardiogram (ECG) and heart rate variability (HRV) signals and intelligent methods. The paper's results showed that combining morphological, linear, and non-linear features can predict the mortality of patients with accuracy and sensitivity of 96.7±6.7% and 94.1±5.8%, respectively. As a result, accurate classification of diseases and correct prediction of patients by reducing unnecessary monitoring can help optimize ICU beds' use. According to new and advanced techniques and technologies, it is possible to predict and treat many diseases in ICU, leading to longer patient survival.

Key Words: *Intensive Care Unit (ICU); Prediction; Mortality rate; Morphological; Linear and non-linear features*

Introduction

Health-treatment methods to maintain patients' health have made undeniable progress [1]. Accurate disease prediction is very valuable in evaluating new treatments, controlling resource consumption, and improving the quality control of intensive care units [2]. Accurate classification of diseases and correct prediction can ultimately help optimize ICU beds' by reducing unnecessary monitoring. With new and advanced techniques and technologies, it is possible to predict and treat diseases in the ICU departments, leading to longer and more patient survival [3]. In this paper, using the morphological parameters of the heart signal, the heart rate variability signal, and the linear and non-linear features extracted from this signal, we predict the mortality of cardiovascular patients hospitalized in the ICU during hospitalization in this department. Also, it is used to predict the future state of the patient until the moments before death.

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Due to the inherent nature of HRV, which is assumed to be a chaotic signal, models, processors, and non-linear quantifiers are used to extract information. They will be used to analyze and evaluate different signals [4]. The use of return maps to predict time series has been developed recently, and good results have been reported [3,5]. In this study, for better and more accurate identification of the period of the risk of death, in addition to the HRV signal information, morphological features of the ECG signal were extracted. This paper aims to investigate the changes in the cardiac signal in two different states: A) from the time of hospitalization in the ICU to a few hours before death and B) from a few hours before death to the moment of death). In previous research, not much attention has been paid to combining the information of ECG and HRV signal features to predict the patient's future condition [1-7]. Therefore, in this research, an attempt is made to simulate a hybrid model and extract suitable parameters of this model. Then, using the parameters obtained from the model, the patient's conditions and the risk of death are predicted.

The rest of this paper is organized as follows. In the next section, we present the data and proposed method. Then simulation result is introduced. Our results based on different approaches are reported here. Finally, we stated the discussion and conclusion in the last section.

Proposed Method

Regarding that the patients admitted to the ICU are considered critical, it is better to correctly record the data from the first moment of hospitalization to predict their future process [1,2]. After recording the required data from the patients and before using them to implement the algorithm, pre-processing must be done. The processes in this part include removing noise and even solving the phenomenon of lack of data. Different filtering techniques can be used according to the desired signal noise, and imputation techniques can be used to solve the missing data [8,9]. Figure 1 shows an ECG signal for 2.5 sec. To generate HRV, after finding the R peaks in ECG, the distance between different R peaks is calculated. Finally, the heart rate is obtained based on Equation 1.

$$HR = \frac{60\ (\text{sec})}{RRI\ (sec)} \tag{1}$$

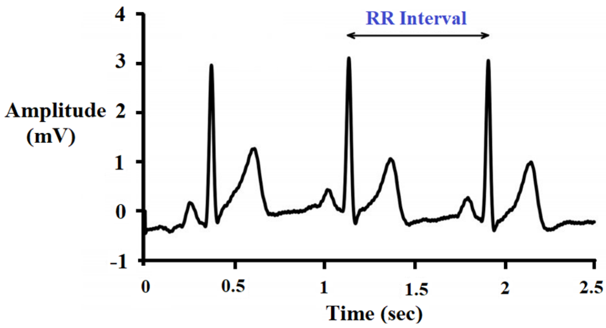

Figure 1) *Cardiac signal and display of R-R interval [9].*

Windowing method

The goal of the signal windowing method is to form different time series. In this method, we can use a window with a width of τ and move this window with an overlap amount of J on the signal [4]. Assuming that the time of death is at the moment *T*, the number of windows equals . The windowing method is shown in Figure 2.

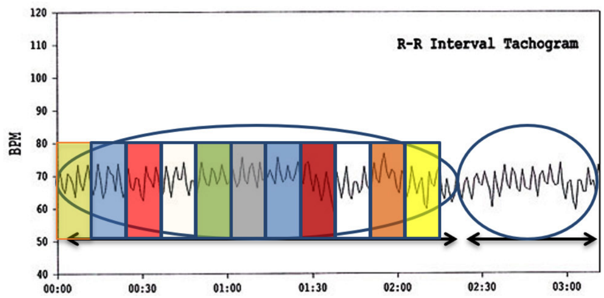

Figure 2) *Signal windowing method.*

In this section, a part of the signal is scanned by using any window with a certain width τ, and to scan other parts of the signal, the window must be slid over it. Suppose it is assumed that the window is located at the beginning of the signal and its width is 500. In that case, the first sample to the 500th sample is placed in this window, and if we consider the overlap of the window as one unit, the data in the second window is from the second sample to 501. Suppose it is assumed that there are 10,000 samples before death. There are 7,000 samples in the first interval (from the moment the patient is admitted to a few hours before death), which means the prediction of death is 3,000 samples before death (if the sampling frequency is 256. Let's consider that it takes about an hour) the number of produced time series will be equal to 9500.

According to the topics discussed above, several time series can be formed using the windowing method, and in each series, the sample from the beginning to the end is clear. Choosing a suitable linear and non-linear model and applying samples makes it possible to obtain some equations in which the model parameters are unknown in each Equation. In the next step, the goal is to find the model's parameters. In other words, the goal is to extract parameters from the model that has maximum compliance with the model.

In this step, the extracted parameters from the data of each window are applied to the model. The number of parameters depends on the model selection. For example, if the model has three parameters, three parameters are obtained per window. Therefore, if the number of windows in this hypothetical example equals 9500, the total number of parameters will be 3×9500. That is, the parameters become a time series. In the next step, these series can be applied to an intelligent algorithm to evaluate and correct the error. You can also check the process of changing parameters over time by plotting these parameters.

Intelligent algorithm

Different methods can be used to determine the parameter values. One of the most used methods is the use of intelligent algorithms. For example, in an artificial neural network, to find model parameters, these parameters should be considered network weights, and the samples in the window are applied to the network. The training algorithm continues until the error reaches the minimum value [10]. For example, in the first window, the first sample up to 499 is given to the network, and the sample output is 500. In the second window, the second sample up to 500 is applied to the network, and the 501st sample is considered the output, and this process continues until the complete scan of the time series. In the end, the coefficients related to each window are obtained for each window. In evaluating the model, the parameters obtained by the intelligent algorithm should be examined. In this section, according to the obtained parameters, a complete model can be used to reconstruct the original signal and calculate the difference between the original and the reconstructed signal.

Two criteria can be used to predict the patients' mortality: The first index: Uses a binary classifier to achieve the greatest accuracy. The prediction output for each patient should be calculated as one (died in the hospital) and zero (survived). The second index: Predicts the percentage of mortality (risk) with the greatest degree of accuracy. For this index, the risk estimate output must be between zero and one. This scoring is based on three criteria: accuracy (Acc), sensitivity (Sen), and positive predictive value (PPV), which are calculated according to Equation 2. True positive (TP), True negative (TN), False positive (FP), and False negative (FN) parameters are defined in Table 1 [11].

$$\begin{aligned}
&Accuracy(\%) = \frac{(TP+TN)}{(TP+FN+TN+FP)} \times 100 \\
&Sensitivity(\%) = \frac{TP}{TP+FN} \times 100 \qquad (2) \\
&PPV(\%) = \frac{TP}{TP+FP} \times 100 \\
&Score\ = \ min\,(Se, PPV)
\end{aligned}$$

TABLE 1
Confusion matrix

		Actual	
		not survive	**survive**
Predicted	**not survive**	TP	FP
	survive	FN	FP

Figure 3 shows the different stages of cardiac signal processing to predict the patient's condition. In this block diagram, the cardiac signal is processed at each stage, and the patient's score is reported. If an error accompanies the result declared by the system during the training phase, the system will be corrected to reduce the error. It can be corrected by modifying the data pre-processing method or the size of the windows, separating the features from each series, combining them, and applying them to the intelligent system.

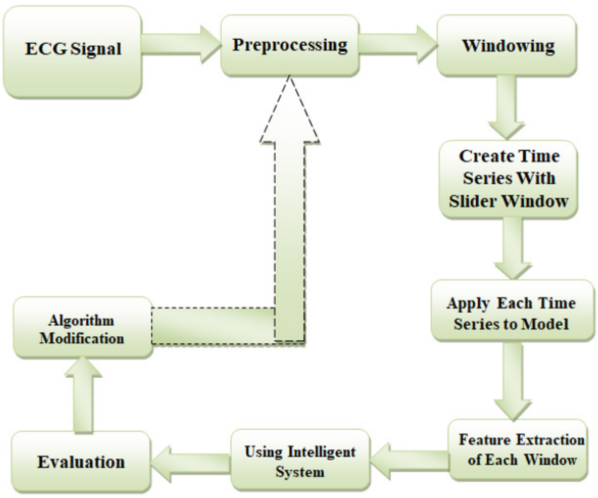

Figure 3) *Block diagram of the proposed method based on time series analysis of different windows.*

Also, Figure 4 shows different linear and non-linear features of the ECG signal in each time window. As you can see in this figure, the features extracted from the heart signal are divided into linear and non-linear categories. In the proposed method, in addition to extracting morphological features from the ECG signal, various features were also extracted from the HRV signal [12-16]. Finally, these features were combined to determine the patient's future condition.

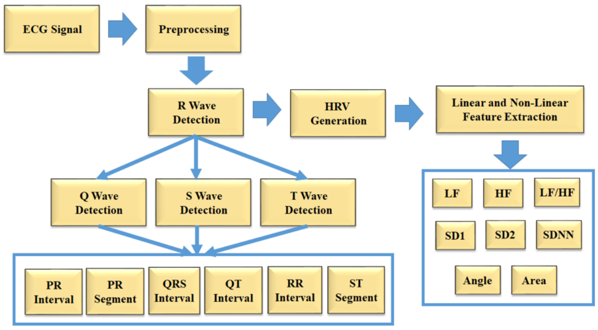

Figure 4) *Block diagram of extracting different linear and non-linear features from ECG signal.*

Result

This paper examined 400 patients, including 200 men and 200 women. Two hundred fifty people (62.5%), and 150 were non-living (37.5%). What will help us in correctly evaluating the extracted information and determining appropriate parameters is choosing a suitable method for the data processing. Different methods are used to model chaotic signals, but what is certain is that the chaotic features of HRV signals and ECG signal features play an important role in predicting the mortality of patients in the ICU. Choosing processing methods that consider its nature can effectively extract its facts. In this research, regarding this issue, chaos measurement criteria and types of chaos models are used for these signals. Using feature extraction, a proper prediction of the future of the signal can be made. Table 2 shows the results of the proposed method for mortality prediction. This table shows that combining morphological, linear, and non-linear features played an important role in achieving a better prediction result. Figure 5 shows the performance comparison of different feature extraction methods. As you can see in this figure, the best results are when a combination of features is used. The use of non-linear features ranked second in terms of patient mortality prediction, and linear and morphological features, as it is clear from this figure, ranked third and fourth, respectively, in terms of evaluation parameters of the prediction model.

TABLE 2

Calculation of sensitivity, positive prediction, and accuracy

Feature type	Sen (%)	PPV (%)	Acc (%)	AUC*
Morphological	73.2±6.5	68.6±5.8	76.5±7.4	0.74
Linear	71.7±7.4	70.1±6.3	74.2±6.8	0.70
Non-linear	89.6±7.9	90.2±8.2	90.9±6.6	0.88
Combination	94.1±5.8	95.7±6.2	96.7±6.7	0.95

AUC*: Area under the curve

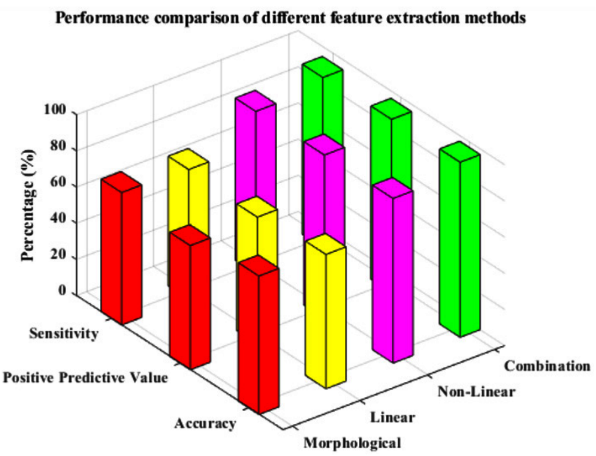

Figure 5) *Comparison of different methods of feature extraction in terms of performance.*

Considering that in this paper, the main focus is on ECG signal and heart rate variability, we should not ignore the recording of other parameters of patients. Therefore, to evaluate and correct the algorithm, it is recommended to use the other data of patients, such as the level of consciousness, the amount of oxygen, carbon dioxide, and even the number of breaths.

Another issue that should be considered is that ICU nurses usually appear at certain time intervals to record some data from the patient on the patient's bed, which may cause problems in patient evaluation. Therefore, key parameters such as heart rate should be recorded continuously, and less important parameters such as body temperature should be recorded discretely, even, if possible, with short time intervals.

Discussion and Conclusion

In this paper, to extract the HRV from the ECG signal, Pan and Tompkins's algorithm was used. In this method, the QRS complex was first identified, and then R wave detection of the complex was addressed. After determining the locations of the R wave, the R-R intervals were calculated, and finally, the HRV signal was formed. Before using the ECG signal, a high-pass filter with a cutoff frequency of 0.6 Hz was employed to eliminate the motion artifacts in the signal. The use of digital bandpass filters in the pre-processing steps of ECG signals to attenuate the input noise is a conventional method in this area [17].

The clinical use of HRV was first proposed in 1965 [18]. In the 1970s, Ewing developed several simple short-term clinical tests to diagnose the autonomic nervous system impairment in diabetic patients by the R-R difference [19]. The clinical significance of HRV became clear in the late 1980s when it was demonstrated that HRV is a strong and independent predictor of death following myocardial infarction (MI) [20]. HRV has several clinical applications; one of its important uses is evaluating the risk of sudden death after a heart attack [19]. Reducing HRV fluctuations is a useful prognosis of mortality and acute problems in patients after acute myocardial infarction. Today, HRV is of great importance in predicting the risk of cardiac death in some diseases, such as cardiac ischemia and myocardial infarction, and the classification and diagnosis of various arrhythmias and heart diseases [21,22].

Taking into account that two factors of the HRV and blood pressure are referred to as the important risk factors of mortality of patients in cerebrovascular intensive care units, the precise prediction of these signals can save the lives of many patients in the intensive care unit. A key point in the innovation of this paper is to predict the future of patients using the influential data in the death of these patients (HRV) and examine the system dynamic changes using a return map. As well as, considering the chaotic nature of the series, the use of chaotic models and maps can be effective in better predicting the patient's future. In this paper, we presented a return map model with a part of the signal and extracted the parameters proportional to this signal. Then, using the obtained map, a true prediction of the patient's future times was proposed. Hence, this study aimed to examine the map parameters and how to change the system's dynamics and compared these results with the time when the system dynamics go to death for predicting the future status of the patient. In addition to the subject of study, one of the latest topics in medical research, one of the main issues that will play a role in its implementation is paying attention to the chaotic nature of the signals and distinguishing the research from other similar studies in this area. Overall, from the perspective of novelty and innovation in the research, items such as the lack of direct need to record many data of the patients, continuous recording of the cardiac signal of the patient, mortality prediction using a return map view, introducing new features of return map to predict the future status of cardiovascular patients in ICU, a new approach in determining the patient's length of stay and prediction horizon to classify and predict the death class, providing a non-linear method to determine the adaptive parameters in different time intervals of stay in ICU, examining the dynamics of the HRV signal by comparing the ratio of near-death time interval changes relative to far intervals can be noted. In addition to predicting mortality in cardiovascular patients, many studies have pointed out the importance of predicting mortality in cerebrovascular patients. The following sections will give you an overview of some of these studies. The method proposed in this paper can help save the lives of cerebrovascular patients by using the risk factors of this disease.

Naver HK et al. [23] followed the idea of whether tests that show cardiovascular sympathetic and parasympathetic behavior can be associated with the direction and area of the brain injury. Therefore, heart rate variability and blood pressure in patients with monofocal stroke were compared with those with ischemic attacks and healthy subjects. A comparison of subjects with left-side stroke with the control group and those with right-side stroke indicated that stroke on the right side was associated with a decline in HRV changes and represented a reaction that takes place under parasympathetic control. The results of this study have revealed that the risk of death has a very strong relationship with the orientation and location of the stroke. High blood pressure plays a crucial role in pathological evaluations of cardiovascular and cerebrovascular mortality in hemodialysis patients. The investigations have demonstrated that high systolic and diastolic blood pressure increases the risk of cardiovascular and cerebrovascular mortality. Systolic blood pressure higher than 180 mm Hg and diastolic blood pressure higher than 90 mm Hg is associated with increasing the risk of death of patients [24].

By examining 24-hour systolic blood pressure, A Fletcher [25] has shown a positive direct correlation between systolic blood pressure and mortality caused by a heart attack and brain stroke. Previously, this positive linear relationship was also reported in other studies. In contrast, diastolic blood pressure still has a linear relationship with the mortality of brain patients and a curved linear relationship with the mortality of cardiovascular patients [26]. Li SJ et al. [27] examined HRV dynamic changes in an acute cerebrovascular accident to determine the risk of stroke. Thirty-five patients were evaluated, and their HRV was recorded 24 hours daily for five consecutive days. In terms of the level of the Glasgow Coma Scale (GCS), patients were divided into two groups. The first group of patients had GCS between 3 and 8, and the second group had GCS between 9 and 15. Of the 35 patients, 17 patients were assigned to the first group, and 18 remaining patients were placed in the second group. Patients in the first group significantly showed a reduction in HRV, the standard deviation of RR intervals, and overall frequency. The HRV chart of the patients has lost its changes in the circadian cycle during a 24-hour and maintained a low-level curve throughout the day. The success rate in predicting the risk of stroke has significantly correlated with the overall frequency, LF, HF, and GCS levels. The mortality prediction rate of these patients was 88.89%, and the survival prediction rate was 82.14%. In 2009, Andrea L et al. [28] studied 18 patients with brain injury. These patients have dramatically observed impaired cerebrovascular reactivity and impaired function of the autonomous nervous system (low power spectrum of HRV). This study reported a significant correlation between impaired cerebrovascular reactivity and the HRV power spectrum. The component of high-frequency HRV can be used to predict brain injury and disorders in the autonomic nervous system. In other words, it can be said that HRV may be intended as an indicator to predict the level of brain damage.

Gianni D et al. [29] showed that non-linear parameters extractable from HRV could provide valuable information for the physiological interpretation of heart rate variability. The two groups were considered among the non-linear parameters associated with HRV fractal behavior. The beta component is taken from the power spectrum and is based on the fractal dimension. To evaluate the relationship between brain injury severity and fractal behavior, 20 patients with stroke and ten healthy subjects were examined. All individuals have a 24-hour ECG recording. The fractal dimension in this study is obtained from the Higuchi algorithm. The results have indicated that fractal analysis has shown interesting information about HRV dynamics in healthy subjects and patients with stroke. The fractal dimension has shown the ability to differentiate between healthy individuals and patients with stroke, even with different lesion severities.

The results of research conducted by Tsivgoulis G et al. [30] showed that high blood pressure is one of the everyday occurrences of acute cerebral ischemia, observed in 80% of patients. The amount of blood pressure has also been correlated with the severity of acute stroke. Günther A et al. [31] researched the infection after the incidence of acute stroke, which is one of the most commonly observed side effects. The project used HRV as an index that reflects changes in the autonomous nervous system to predict the infection after stroke. Forty-three patients with acute stroke were examined. The acute infection in these patients was predictable without taking blood factors and solely based on the features extracted from the HRV so that patients with infection showed an increase in HF, a decrease in LF and LF/HF during the day decline in LF and VLF during the night. Graff B et al. [32] analyzed the ECG of 75 patients with ischemic stroke. The linear and non-linear parameters of HRV and blood pressure, and respiration rate of these patients were evaluated. The mean RR interval, amount of blood pressure, and blood pressure changes showed that the increase in these parameters could be a good indicator for identifying an ischemic stroke.

Caroline A et al. [33] reported that arterial blood pressure and cerebral blood flow could be used as markers for cardiovascular problems. An increase in each can increase the risk of stroke in any of the regions. Yamaguchi Y et al. [34] researched the relationship between heart rate variability and the development of cerebrovascular disease. This study examined heart rate variability and night-time heart rate drop. The Root Mean Square of the Successive Differences (RMSSD) rate in patients with progression of cerebrovascular disease was higher than those without disease progression.

Moreover, the amount of RMSSD at night was completely independent of the incremental trend of disease progression. The drop in heart rate variability in the early hours of the night was lower. Eventually, the increase in HRV during the night is considered an indicator to predict the spread of cerebrovascular disease.

Sung-Chun Tang et al. [35] employed the non-linear features of HRV to predict the risk of occurrence of acute stroke in patients admitted to the intensive care unit. Multiscale entropy of patients with stroke was obtained from an hour of recording the ECG signal from patients in the ICU. The complexity index is also considered the area under the multiscale entropy curve. The behavioral process of the multiscale entropy graph of patients with arterial fibrillation was quite different from the patients who did not have this problem and the control group. Besides, the complexity index was significantly lower in patients with arterial fibrillation. This research has shown that patients admitted to the ICU with an acute stroke can be distinguished from those without arterial fibrillation using the non-linear features extracted from the HRV signal.

Assessing the patient's mortality risk and informing the patient's relatives can be a tool for evaluating the quality of ICU services and checking the success rate of applied treatments [4]. In previous research, most researchers have focused on using software developed in the field of mortality prediction in the intensive care unit and methods based on artificial intelligence [1,4,5,36,37]. The results show that the software is susceptible to the recorded data and the completeness of the data. For example, the results obtained from the data analysis of patients hospitalized in the special care department of different hospitals are visibly different from this software. In American hospitals, the software is implemented based on standard data, which differs in setup from other hospital units worldwide [38].

In addition to the research topic, one of the newest topics in medical research, one of the most important issues that will play a role in the process of its implementation is the attention paid to the chaotic nature of signals. This makes the research different from other similar research in this field. Choosing the appropriate processing methods that can identify and separate the nature of the proposed signals through feature extraction from the signal is one of the important topics in research related to this field. So that today, most of the research is dedicated to finding high-efficiency processing methods. In the meantime, the inherent complexity of chaotic signals has increased attention to slightly chaotic descriptors that can display signal dynamics. Among others, we can mention the use of complexity criteria and the calculation of various temporal and spatial dimensions, such as the correlation dimension and coherence calculation, to check the complexity of these signals.

In the field of artificial intelligence, such as neural networks, genetic algorithms, etc., research has been conducted in recent years. The main problem with these methods is using parameters recorded in the intensive care unit, which causes inefficiency. It is networked and reduces the speed of convergence. Therefore, there is a need to examine the effective factors and select the effective features. Since heart rate variability and blood pressure are two important risk factors for the death of patients in cardiovascular and cerebrovascular intensive care units [39,40], accurate prediction of these signals can save many lives. Save the patients in this special care department. Considering that the mentioned series are chaotic, using chaotic models and maps can effectively predict the patient's future. Since signal-to-image conversion methods such as ECG imaging [41] can effectively identify cardiac diseases, this technique can be used to identify patients' conditions better when they are nearing death.

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