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Predicting the Death of Cerebrovascular Patients Admitted to Intensive Care Units

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Abstract

Background: This article aimed to explore the mortality prediction of cerebrovascular patients in the intensive care unit (ICU) by examining the important signals associated with these patients during different periods of admission in the intensive care unit, which is considered as one of the new topics in the medical field. Several approaches have been proposed for prediction in this area that each of these methods has been able to predict the mortality somewhat, but many of these techniques require the recording of a large amount of data from the patients, where the recording of all data is not possible in most cases; while this article focuses only on the heart rate variability (HRV) and systolic and diastolic blood pressure.

Methods: In this paper, using the information obtained from the electrocardiogram (ECG) signal and blood pressure with the help of vital signal processing methods, how to change these signals during the patient's hospitalization will be initially checked. Then, the mortality prediction in patients with cerebral ischemia is evaluated using the features extracted from the return map generated by the signal of heart rate variability and blood pressure. To implement this paper, 80 recorded data from cerebral ischemic patients admitted to the intensive care unit, including ECG signal recording, systolic and diastolic blood pressure, and other physiological parameters are collected. Time of admission and time of death are labeled in all data.

Results: The results indicate that the use of the new approach presented in this article can be compared with other methods or leads to better results. The accuracy, specificity, and sensitivity based on the novel features were, respectively, 97.7, 98.9, and 95.4 for cerebral ischemia disease with a prediction horizon of 0.5-1 hours before death.

Conclusion: The perspective of the prediction horizons and the patients' length of stay with a new approach was taken into account in this article. The higher the prediction horizon, the nurses or associates of patients have more time to carry out therapeutic measures. To determine the patient's future status and analysis of the ECG signal and blood pressure, at least 7.8 hours of hospitalization is required, which has had a significant reduction compared with other methods.

Keywords: Death Prediction, Intensive Care Unit (ICU), Heart Rate Variability (HRV), Systolic and Diastolic Blood Pressure, Return Map

1. Background

The mortality rate from cardiovascular and cerebrovascular diseases is one of the leading causes of death in industrialized countries [1]. The intensive care unit (ICU) is a special place where medical personnel and equipment are employed for the treatment and management of critically ill patients. An acceptable target in this section is to save the lives of survived patients because all patients admitted to the ICU would not return to normal life and perhaps the life, and some patients will die due to the severity of the disease [2]. The intensive care unit should not be considered as a place for the death of patients. Therefore, the selection of patients for hospitalization in the ICU is essential because it is of great importance in maintaining the spirit of the nursing staff. As well as, considering that the cost of admission to ICU is very high, patients should be selected for admission to this department who need intensive care, and there is hope for their recovery. Because many factors influence ICU, thus providing proper care and treatment can have a positive effect on the disease process [3]. Millions of deaths annually occur around the world that, by providing the right services in the intensive care unit, may be reduced to an acceptable level. In addition to monitoring and treating the critically ill patients, intensive care unit physicians are responsible for predicting the outcome of patients and identifying and differentiating patients who take special use of the ICU, because, as noted, not all patients admitted to the ICU do not necessarily benefit from this section, and hospitalization for some patients will only lead to a more convenient death [4].

Calculating the risk and predicting the patient's future status, especially in costly settings, are of great importance. The mortality prediction of patients, while informing nurses and associates, can be a means for evaluating the quality of ICU services, as well as assessing the success rate of treatments applied. For this purpose, various techniques with engineering and medical approaches have been designed and provided. These methods are designed to quantify and reduce the number of separated features and convert them into a unit quantity so that this unit quantity is associated with the severity of the disease and the conditions of the patient [5].

Critically ill patients who are in a serious and critical condition and cannot take any care of themselves and those patients with impaired vital systems of the body are admitted to the ICU. Among patients admitted to the ICU, an important group is cerebrovascular patients who require constant monitoring of vital signs, especially heart rate and blood pressure, since these two parameters have a crucial role in the mortality of patients. This group of patients includes ischemic stroke (blocking of blood vessels to the brain (87%)), hemorrhagic stroke (rupture of blood vessels near the brain (13%)), and so on [6].

1.1. Heart Rate Variability (HRV)

Heart Rate Variability (HRV) is among the important parameters in predicting mortality rates that should be specifically taken into account. The HRV signal is a non-invasive tool to assess cardiovascular, cerebrovascular systems, and autonomic nervous system [7]. In the past two decades, strong relationships between autonomic nervous system activity and mortality due to brain diseases have been found. Many experiments have revealed that there is a correlation between cerebrovascular disease and increased sympathetic activity or reduced vagal activity, and these results have led to advances in the detection of autonomic nervous system activity. The HRV is one of the very good indices for this detection. The non-invasive and relatively easy measurement has become an appropriate criterion for this purpose. Today, many commercially available medical equipment automatically measures heart rate variability. The form and size of the various waveforms of the ECG signal resulting from the recording of the bioelectric activity of the heart is a very proper source for the

diagnosis of health or diseases associated with arteries [8]. In ICUs, the condition of many patients cannot be easily controlled, and monitoring of physiological signals is carried out continuously for them so that the current situation and any signs of danger could be under medical care. Because the condition of these patients may be very serious when these symptoms were viewed, a device or system that can predict these changes and give an early warning to physicians can be very valuable.

Investigations have demonstrated that some diseases affect HRV rather than influencing the ECG form [9]. HRV means changes at intervals between consecutive heartbeats. In other words, the time series obtained from calculating the intervals between two successive R waves in the ECG signal constitute the HRV signal [3]. In Figure 1, how to extract the HRV from the ECG signal is represented.

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 [10].

The clinical use of HRV was first proposed in 1965 [11]. In the 1970s, Ewing developed a number of simple short-term clinical tests to diagnose the autonomic nervous system impairment in diabetic patients by the R-R difference [12]. 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) [13]. HRV has several clinical applications; one of its important uses is the evaluation of the risk of sudden death after a heart attack [12]. The reduction of HRV fluctuations is a useful prognosis of mortality and acute problems in patients after acute myocardial infarction (MI). Today, HRV is of great importance in predicting the risk of cardiac death in some diseases, such as cardiac ischemia and myocardial infarction, as well as the classification and diagnosis of various types of arrhythmias and heart diseases [14].

1.2. Blood Pressure

The pressure of the blood in the circulatory system, often measured for diagnosis since it is closely related to the force and rate of the heartbeat and the diameter and elasticity of the arterial walls. The highest pressure (systolic) is caused due to contraction of the heart, and the lowest pressure (diastolic) occurs at the time of filling the heart. The main complication of high blood pressure is the increased risk of the occurrence of cerebrovascular diseases [15]. The severity of the complications depends on race, sex, hyperlipidemia, diabetes, and so on. The most important vulnerable members of hypertension (high blood pressure) are the heart, brain, and kidneys. Although researchers have identified hypertension as a risk factor for mortality from cerebrovascular disease, systolic blood pressure is the best predictor of the risk of developing cardiovascular diseases [16]. During their investigations, the researchers have concluded that increased systolic blood pressure is the most important parameter for the mortality prediction caused by cerebrovascular diseases in a wide range of ages. In this regard, a prospective study was carried out on 53,000 participants at the Center for Health Studies. In a follow-up period of 5 to 7 years, they faced the 459 deaths from vascular diseases. By examining the victims, they concluded that an increase in systolic blood pressure has a greater impact on developing vascular diseases than diastolic blood pressure, both in young and older people [17].

In examining the patient's blood pressure, systolic blood pressure indicates how the heart works during the beating hard, while diastolic blood pressure represents the pressure of the large arteries during heart relaxes between the beatings. Meanwhile, the amount of systolic

blood pressure to check the effect of blood pressure on the mortality of these patients is of special importance. It has been proven that patients with high systolic blood pressure are more exposed to developing the fatal complications of cardiovascular and cerebrovascular diseases than those with high diastolic blood pressure. Thus, in predicting the risk of cardiovascular and cerebrovascular diseases, systolic blood pressure should be taken into consideration more than diastolic blood pressure [18-19].

In previous studies, the researchers focused more on the use of software made in the field of mortality prediction in the ICU and artificial intelligence-based techniques. The results reveal that the use of the software is highly sensitive to data recorded and also their completeness. For example, the results obtained from analyzing the data of patients admitted to the ICU of different hospitals are remarkably different via this software. This is due to the implementation of software-based on standard data recorded in USA hospitals, which is different from various hospital wards in other parts of the world in terms of Setup [20-21].

In the field of employing artificial intelligence such as neural networks, genetic algorithms, and etc., investigations have also been performed in recent years. The main problem with these methods is the use of numerous recorded parameters in the intensive care unit, which leads to inefficiency in the network and reduces the speed of convergence. Therefore, the need to examine the effective factors and somehow select effective features is felt.

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 article is to predict the future of patients using the influential data in the death of these patients (systolic and diastolic blood pressure, HRV, or a combination of them) 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 prediction of the patient's future. In this paper, we intend to model a return map with a part of the signal and extract the parameters proportional to this signal. Then, using the obtained map, a true prediction of the patient's future times can be proposed. Hence, the aim of this study is to examine the map parameters and how to change the dynamics of the system and compare 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, which is one of the latest topics in the field of medical research, one of the main issues that will play a role in the process of its implementation is to pay attention to the chaotic nature of the signals. This distinguishes 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 systolic and diastolic blood pressure of the patient, mortality prediction using a return map view, introducing new features of return map to predict the future status of cardiovascular and cerebrovascular patients in ICU, a new approach in determining the patient's length of stay and prediction horizon in order 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. Naver HK et al. [22] 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 a group of patients with monofocal stroke were compared with a group of patients with ischemic attacks and healthy subjects. A comparison of subjects with left side stroke with the control group and those who had a right-side stroke indicated that stroke on the right side was associated with a decline in HRV changes. This represents 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 results of investigations have demonstrated that both high systolic and diastolic blood pressure will increase 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 [23].

By examining 24-hour systolic blood pressure, A Fletcher [24] in his study has shown that there is 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 [25].

Li SJ et al. [26] 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 a day for 5 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 level. The mortality prediction rate of these patients was 88.89%, and the survival prediction rate was 82.14%.

In 2009, Andrea L et al. [27] studied 18 patients with brain injury. Impaired cerebrovascular reactivity and impaired function of the autonomous nervous system (low power spectrum of HRV) have been dramatically observed in these patients. In this study, a significant correlation between impaired cerebrovascular reactivity and the HRV power spectrum has been reported. 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. [28] showed that non-linear parameters extractable from HRV could provide valuable information for the physiological interpretation of heart rate variability. Among the non-linear parameters associated with HRV fractal behavior, the two groups were more taken into account. The beta component is taken from the power spectrum, and the component that is based on the fractal dimension. To evaluate the relationship between brain injury severity and fractal behavior, 20 patients with stroke and 10 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. Fractal dimension has shown the ability to differentiate between healthy individuals and patients with stroke even with different severities of the lesion.

The results of research conducted by Tsivgoulis G et al. [29] showed that high blood pressure is one of the common 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. [30] carried out research on the infection after the incidence of acute stroke, which is one of the most commonly observed side effects. In the project, they used HRV as an index that reflects changes in the autonomous nervous system to predict the infection after stroke. 43 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 high frequency (HF), a decrease in low frequency (LF), and LF/HF during the day, and decline in LF and very low frequency (VLF) during the night.

Graff B et al. [31] 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. [32] reported that arterial blood pressure and cerebral blood flow could be used as markers for cardiovascular problems, and an increase in each of them can increase the risk of stroke in any of the regions.

Yamaguchi Y et al. [33] researched the relationship between heart rate variability and the development of cerebrovascular disease. In this study, heart rate variability and night-time heart rate drop were examined. The rate of Root Mean Square of the Successive Differences (RMSSD) 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 as an indicator to predict the spread of cerebrovascular disease.

Sung-Chun Tang et al. [34] 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 as 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, as well as with 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 the patients without arterial fibrillation using the non-linear features extractable from the HRV signal.

This article is designed as follows:

In the second section, features extraction methods from ECG and HRV signals are examined to quantify the patient's condition at different times of admission to the intensive care unit. Then, we examine the return map created from the vital signals and introduce several new features of this map used in this paper, as well as the measurement and evaluation criteria of prediction methods. Furthermore, important indicators in the mortality prediction of patients are presented, and standard definitions are provided to create an acceptable prediction algorithm. At the end of this section, the database used in this article, along with the necessary pre-processing for them, is explained. In the third section, the investigation of the results of using the features defined in the third section and the effectiveness of each feature is presented to calculate the mortality prediction rate and the optimum prediction horizon. Then, to achieve better prediction results, the combination of features has been examined considering the degree of specificity, sensitivity, prediction horizon, and initial length of stay of patients to determine the future status. In the fourth section, the summary and conclusion of the proposed method and suggestions to complete it in the future are provided.

2. Methods

2.1. Database

To evaluate the results of implementing the mortality prediction algorithm of cerebrovascular patients, 88 individuals with the cerebral ischemic disease with an average age of 68 ± 8 (years), an average weight of 86 ± 13 (kg), and an average height of 169 ± 11 (cm), who had

a history of cardiovascular disease, were used. With the assumption of 6% mortality rate [35, 36], a confidence level of 0.95, and a maximum marginal error of about 0.05, the sample size was calculated at least 88 subjects. 48 patients (55%) were men, and 40 others (45%) were women. All patients were under medical care from the initial length of stay in ICU, and the ECG signal and their systolic and diastolic blood pressure were recorded continuously. As well as, other physiological parameters of patients such as respiration rate, body temperature, blood oxygen saturation percentage, etc. were monitored by a monitoring device specific to each patient.

2.2. Feature Extraction

Today, the quality of optimal feature extraction methods of the vital signal is of great importance in the field of vital signal processing, prediction, detection, or classification of a disease. The feature extraction from the signal, in general, can be divided into linear and non-linear methods. In linear methods, the total amount of variation is calculated via statistical methods. The linear methods can be divided into time domain and frequency domain methods. One of the main advantages of these features is the simplicity of their calculations. Of course, the statistical features depend, to some extent, on the quality of the recorded data that the quality may be affected by environmental noise. The time-domain methods are among the simplest analysis methods of the HRV signal and blood pressure, which are classified into two groups of statistical and geometric measurements. Because heart rate and blood pressure monitoring in the cerebrovascular disease of the intensive care unit is very important, so determining the statistical characteristics of these signals, including mean and variance, can be helpful as an adjunct in analyzing the behavior of the signals in these patients. The features of this area include the standard deviation of NN intervals (SDNN), the standard deviation of the average of NN intervals in all, the root mean square of successive difference (RMSSD) [2].

The frequency components of the HRV are different. Its three main frequency components include VLF, LF, and HF [37]. The fluctuations of these two components represent sympathetic and parasympathetic activity, and the ratio of these two components is considered as a measure of sympathetic and parasympathetic function balance, which is used as a feature. Previous studies have revealed that high frequencies in the HRV signal power spectrum represent the activity of the parasympathetic part of the nervous system as well as low frequencies indicate the activity of the sympathetic part of the autonomic nervous system that controls heart rate [38]. Note that the indices resulting from the difference in neighboring R-Rs indicate high-frequency changes or short-term changes. Thus, the ratio of signal energy in the low-frequency band to the signal energy in the high-frequency band (LF/HF) is an important feature in the frequency domain that determines the balance of sympathetic and parasympathetic (sympathovagal) function [39] and is used in this article as one of the frequency domain features.

It is assumed that the time series of R-R intervals are in the frequency domain are static; that is, variations are harmonic and sinusoidal. Indeed, heart rate variability can be periodic (due to breathing) and non-periodic (due to sudden changes in the environment or individual state). Therefore, HRV can be evaluated due to the complexity and dynamic interaction of biological signals using non-linear methods.

In recent years, due to the chaotic behavior of the cardiovascular and cerebrovascular system, non-linear methods have been used in the analysis of the heart rate signal. One of these techniques is the Poincare plot. This method was first employed as a qualitative tool, and later quantification of the Poincare plot geometry was proposed. Tulppo M et al. [40] put an ellipse on the Poincare plot to calculate the indices of heart rate. Brennan et al. [41] showed that the width of the Poincare plot represents the level of short-term changes in the heart rate signal.

The two parameters of SD_1 and SD_2 in this plot are used to see how the heart rate variability. The SD_1 is related to rapid changes of NN in data, mainly associated with the respiratory sinus arrhythmia (RSA), while SD_2 describes long-term changes in RR (i). The ratio of SD_1/SD_2 can also be calculated to describe the relationship between these components [42]. The SD_1 and SD_2 values of the Poincare plot directly depend on the statistical values of the standard deviation of the heart rate signal and the standard deviation of the two successive intervals of the R-peak. Because the SD_1 and SD_2 features cannot show the time dynamic of the VHR signal in a return map well, with presenting a new return map, Karimi et al. introduced the features of angle (α), area (A), the shortest distance of each point relative to the 45-degree line (Shd), increasing (I), decreasing (D) and no change (NC) trends of return map vectors that demonstrate the time changes of the signal with a better accuracy [43]. Another non-linear method for signal processing is to use a recurrence plot. If only the time series $x(i)$ is available, then the Taken's delay embedding theorem can be used to reconstruct the phase space [44]. Accordingly, the trajectory of $\vec{x}$ is reconstructed from the time series $x(i)$ and according to equation (1):

$$\vec{x}_i = [x(i), (i + \tau), \dots, x(i + (m - 1)\tau)] \quad (1)$$

Where m is the reconstruction dimension τ of time delay. A common method for determining the dimension of reconstruction is the false nearest neighbor (FNN) approach, and for the delay is the mutual information (MI) [45].

To determine the number of independent variables necessary to describe the behavior of the system, the correlation dimension that provides a level of complexity of the system is used. The determined linear system has the integer correlation dimension, while the correlation dimension of chaotic systems is fractional. But a random system can have the integer dimension and the fraction dimension. Several features have yet been presented for the quantitative evaluation of the recurrence curves. These features include the mean length of the diagonal lines ($LMean$), the maximum length of the diagonal lines ($VMax$), the entropy of the diagonal lines ($ENTR$), the maximum length of the vertical lines ($LMax$) and the trapping time (TT) [43]. Then, in order to enhance the efficiency of the system in predicting the future condition of cerebral ischemic patients, the features of systolic and diastolic blood pressure including maximum systolic blood pressure ($SBPMax$), minimum systolic blood pressure ($SBPMin$), maximum-minimum (differences) in systolic blood pressure ($SBPMax-Min$), mean systolic blood pressure ($SBPMean$), maximum of the average squared difference between successive measurements for systolic blood pressure ($SBPSVMax$), maximum diastolic blood pressure ($DBPMax$), minimum diastolic blood pressure ($DBPMin$), maximum-minimum difference in diastolic blood pressure ($DBPMax-Min$), mean diastolic blood pressure ($DBPMean$), maximum of the average squared difference between successive measurements for diastolic blood pressure were used.

2.3. Introducing prediction criteria in the mortality of patients

In this paper, different methods have been used to examine the mortality prediction rate of cerebrovascular patients. The objective of all these methods is to achieve the desired results so that more detailed information to better take into account the patients' future status can be provided to nurses and physicians. Hence, there is a need to define standards in this regard. One of the important criteria is the false positive rate (FPR) or false alarm rate. This measure means that to what extent a system or algorithm designed for prediction can discover the right time that the patient goes to death. That is, the lower this criterion is, the power and

efficiency of the algorithm in the debate of prediction will be somehow higher. The second point that should be considered as an important criterion is the rate of forecast horizon (FH). The forecast horizon is the length of time into the future for which forecasts are to be prepared. This measure represents the alarm time to nurses and doctors and specifies how long this alarm will be given before death. Certainly, the higher the rate of this index, the efficiency of the system will be better, and physicians and nurses will have more opportunities to provide more facilities to the patients and take more care measures. Another measure that should be defined in the mortality prediction of cardiovascular patients is the length of stay (LOS) to predict the future condition of patients. This means how long the hospitalization of the patient should be passed so that the future status of the patient to be examined. Figure 2 graphically illustrates the above-mentioned criteria on the heart rate variability signal.

To determine the effectiveness of the proposed algorithm, the patient's conditions in the length of stay are required to be carefully evaluated, and the results of the proposed mortality algorithm should be reported with appropriate analysis. In the suggested method of this paper, initially, due to the effect of the patient's HRV signal on the mortality of cerebrovascular patients, this signal was divided into windows with different intervals (the results of optimal prediction determined the final desired window size). First, the algorithm for determining the true prediction of death was evaluated. The true prediction of death using the proposed algorithm means that if the interval in which the patient correctly goes to death, the true alarm should be given.

The mean interval from which the patient goes to death is that, after this interval, death will surely occur. Considering that death happens during the patients' length of stay until death, the prediction of this interval is of high importance because the lack of predicting this interval is associated with the patients' lives. Therefore, as the number of TN (True Negative) and TP (True Positive) is higher, the result will be better. TN means that the patient does not really go to death and is correctly identified, while TP means the patient really goes to death, and the proposed algorithm correctly predicted it. Now, if there is a case in which the patient is in an interval that is going to the death in reality, but the system does not identify it, such cases are FN (False Negative). And if the patient is in the normal state and has not yet reached the death interval, but the system falsely identifies the death interval, FP (False Positive) cases will be recorded. If the number of FP in the length of stay is high, this can be distressing for the patient, because the number of false alarm means the patient's arrival to the death interval and a great mental burden is imposed on the patient. Therefore, the prediction system should, as far as possible, have the minimum desired false positive rate (FPR) in the length of stay. As a result, the selection of appropriate measures to predict mortality should be in line with declining the FPR. The aim of this article is the use of different approaches to achieve the desired false positive rate (FPR) in the patients' length of stay. Another important point that should be taken into account is that if the prediction system has a low false alarm (i.e., it correctly declares that the death interval is not reached) but it cannot properly alarm when the patient is entering the FH interval, this could also undermine the effectiveness of the prediction system. That is, the system is unable to identify the death interval, but it can predict the fact that the patient is not in the death interval. Given that the threshold criterion at different time intervals to achieve the sensitivity is used in these methods, it can be concluded that as the sensitivity is higher, the selected threshold will be more favorable. Thus, the threshold level to achieve a higher sensitivity should be changed in the proposed method of this paper.

2.4. Model Evaluation

A mortality prediction model is used in the ICU to classify patients into different risk classes. A good mortality prediction model makes a stratification of the risk levels of the patients

admitted to ICU. The proposed model generally creates a numerical estimate of the risk-based on extracted physiological parameters. This model could be valuable clinically because providing a specific model for predicting patients at-risk is a necessity for improving clinical care. Therefore, developing a precise prediction model of the future condition of ICU patients for the nurses and doctors could provide more equipment and facilities to save their lives. To identify that the proposed prediction model is applied for this purpose, the best performing models must be identified.

In assessing whether a presented model is adapted to a dataset, different tests of fit can be used. The goodness of fit index (GFI) of a prediction model shows how well it fits a set of data.

The proportion of covariance in a sample data matrix, which can be explained by the model, is assignable by GFI. Its range is usually between zero and one, and a value closer to one (GFI>0.90 or 0.95) indicated that the model is appropriate [46, 47]. The GFI is calculated using the equations (1) [47].

$$GFI = 1 - \frac{F_d}{F_i} = 1 - \frac{\chi_d^2}{\chi_i^2} \quad (1)$$

Where χ_d^2 is the Chi-Square of the desired model, χ_i^2 is the Chi-Square of the initial model, and F is the corresponding minimum fit function value. In this paper, the GFI obtained to evaluate the prediction model was 0.968. The GFI obtained is the best value of the fit index for the presented prediction model.

3. Results

In this section, the results of the proposed algorithm for predicting mortality in patients with cerebral ischemia are presented. Given that blood pressure and heart rate are two important factors affecting the mortality of patients with cerebral ischemia [48], these two factors have been used to calculate the prediction mortality rate in these patients. Changes in blood pressure and heart rate of subjects under study in this article were analyzed at intervals close to death.

First, the normality of the data was examined by the Kolmogorov-Smirnov test (KMT). After SPSS software analysis in the Kolmogorov-Smirnov test output, if the test was not significant, the p was higher than 0.05, it means that the distribution is normal, and we should use the parametric test. Because the significance level of the test was higher than 0.05 (the minimum of significance level for two groups by KMT was 0.12 and 0.18), therefore the research data were normal and qualified to use the paired sample t-test.

As can be seen in Table 1, the mean systolic and diastolic blood pressure at intervals close to death and beyond death does not show a significant difference using the statistical analysis of paired sample t-test.

To calculate the P-value, we first divided the HRV signal and blood pressure into half-hour windows [50] and then extracted different features from these windows. We calculated the mean and standard deviation of the features obtained from different intervals. Due to the fact that each patient was being compared to him (her) self, the paired sample t-test was used to determine the significance between the features of two consecutive windows. Equation (2) shows how to do the windowing method and calculate the features of each window to determine the P-value.

$$\begin{array}{l} \text{time series} \\ \text{for each window} \end{array} \left\{ \begin{array}{l} W_1: x_{11}, x_{21}, x_{31} \dots, x_{N1} \\ W_2: x_{12}, x_{22}, x_{32} \dots, x_{N2} \\ \vdots \\ W_M: x_{1M}, x_{2M}, x_{3M} \dots, x_{NM} \end{array} \right. \begin{array}{l} \text{different angles} \\ \text{for each window} \end{array} \left\{ \begin{array}{l} W_1: \alpha_{11}, \alpha_{21}, \alpha_{31} \dots, \alpha_{(N-2)1} \\ W_2: \alpha_{12}, \alpha_{22}, \alpha_{32} \dots, \alpha_{(N-2)2} \\ \vdots \\ W_M: \alpha_{1M}, \alpha_{2M}, \alpha_{3M} \dots, \alpha_{(N-2)M} \end{array} \right. \begin{array}{l} \text{mean} \pm \text{variance} \end{array} \left\{ \begin{array}{l} \alpha_1 \pm \beta_1 \\ \alpha_2 \pm \beta_2 \\ \vdots \\ \alpha_M \pm \beta_M \end{array} \right.$$

(2)

Where N, the number of samples in each window, M, the number of windows, α_{1M} is the first angle feature generated of M^{th} window, α_M and β_M are the mean and standard deviation of angle feature in M window.

However, the changes in maximum and minimum systolic and diastolic blood pressure have significant changes at the time of entry into the death intervals. Therefore, as the patient is close to the time of death, systolic and, diastolic blood pressure is increased, and the dynamics of the HRV signal is reduced. Hence, these features can be used as inputs for the mortality prediction algorithm. It should be noted that the use of the maximum and minimum of blood pressure cannot cause many differentiation power and give a precise and special alarm to the mortality prediction system in order to enter the risk of death interval because the systolic and diastolic blood pressure during the length of stay may be increased for the moment due to physiological and psychological changes in patients, but the changes in these two pressures can be very important at different intervals.

Table 1. Extracted features from blood pressure and return mapping of HRV signal in patients with cerebral ischemia

Before death (h) Feature type	2.5-2 (h)	2-1.5 (h)	1.5-1 (h)	1-0.5 (h)	P-Value
SBPmax	174.24±34.41	177.24±52.72	178.24±70.93	190.24±62.74	0.012
SBPmin	122.18±26.02	121.17±19.93	120.18±48.12	113.21±65.92	0.032
SBPmax-min	57.22±16.36	58.22±73.54	60.23±47.12	82.29±56.81*	0.001
SBPmean	144.17±21.95	143.18±4.11	144.18±7.02	144.18±26.17	0.063
SBPsvmax	52.23±15.94	52.44±15.18	49.23±14.15	37.13±12.27*	0.003
SBPSD	14.40±5.94	14.40±6.03	14.40±6.57	15.50±6.89	0.037
DBPmax	97.14±23.73	98.14±54.42	101.15±61.27	113.21±64.43	0.016
DBPmin	63.12±22.17	62.12±21.66	61.12±19.28	50.14±16.37	0.022
DBPmax-min	36.15±10.32	38.16±11.31	39.16±12.47	63.27±18.67*	0.000
DBPmean	81.11±31.25	82.11±31.47	80.10±28.29	77.11±27.13	0.041
DBPsvmax	24.11±8.42	25.12±8.81	27.13±8.91	44.23±12.45*	0.002
DBPSD	8.20±3.13	9.31±3.36	9.32±3.34	10.45±4.14	0.052
α	23.74±8.26	19.70±6.76	18.69±5.41	10.38±3.98*	0.003
A	103.79±28.87	95.79±25.54	88.78±20.32	67.51±15.26*	0.002
*: p<0.005					

How to change the values of the extraction features of the blood pressure and heart rate signal, including SBP max-min, SBP svmax, DBP max-min, DBP svmax, α , and A at various time intervals for patients with cerebral ischemia, are shown in Figure 3.

As specified in this plot, the values of the SBP svmax, α , and A features showed a significant reduction from 0.5-1 hours before death compared to 1-1.5 hours of it. As well as the values of the SBP max-min, DBP max-min, and DBP svmax features have also had a significant mutation from 0.5-1 hours before death compared to 1-1.5 hours of it. Therefore, considering the high differentiation power of these features, they can be used to predict the future status of patients with cerebral ischemia. Thus, it can be hoped that these features will also improve the accuracy, sensitivity, and specificity of the prediction system for death in patients with cerebral ischemia.

Then, according to the introduction of the features that could represent a significant differentiation in near-death intervals, the performance of the mortality prediction system in patients with cerebrovascular disease was examined. First, about the selected threshold for each feature separately, we explored the changes in the various time intervals of hospitalization to the death of the patients. The best result obtained was related to the use of the SBP svmax feature, which was able to obtain the specificity and sensitivity of 78.14%

and 73.34% at the testing phase, respectively. Since the use of each feature separately ignores the system's performance in observing the process of other physiological changes, the combination of the features as discussed in the next step. The best combination of features with an adaptive threshold for each feature was related to the use of the SBP svmax, DBP max-min, and A features. The specificity of the training and testing steps was 90.86% and 83.86%, respectively. As well as the number of false alarm hours to the patient also had the highest amount in both the training and testing phases, which was calculated to be 10.94 and 6.18 hours, respectively, per 24 hours a day that; this parameter can be very important for the patients and the medical staff. Thus, according to the results, using the combination feature mentioned in the training and testing phase, it can be said that the system with the forecast horizon of half-hour before death will issue a false alarm of death at 2.19 times and 3.88 times, respectively, during a day.

Subsequently, to assess the function of the system in predicting the risk of death intervals of patients with cerebral ischemia, the sensitivity of the system to the time when the patient goes to death was examined using the combination of features described above. The sensitivity of the system in the prediction of death time interval, in which the combination feature of the adaptive threshold was used, was obtained to be 88.87% and 80.12% at the training and testing stages, respectively. Figure 4 illustrates the comparison of the level of specificity and sensitivity of the mortality prediction system in the testing phase for patients with cerebral ischemia.

3.1. Extraction of more efficient features

To achieve better results for predicting the mortality in patients with cerebral ischemia, other linear and non-linear features that could provide more contained information about the vital signals of patients were used. All features extracted from the signal of HRV and blood pressure introduced in Section 2.2 are represented in Table 2. First, the value of each feature was calculated at different time intervals. Then, to make differentiation and to find out the amount of information contained in each feature, relative to other features, the value of each feature's information was evaluated using the mutual information (MI) and the genetic algorithm (GA).

Table 2. Types of HRV and blood pressure features extracted from cerebrovascular patients

Feature	Symbol	Feature	Symbol
SDNN	F1	ENTR	F20
SDANN	F2	α	F21
RMSSD	F3	A	F22
LF	F4	ShD	F23
HF	F5	I	F24
LF/HF	F6	D	F25
SD1	F7	Nc	F26
SD2	F8	SBP_{Max}	F27
SD2/SD1	F9	SBP_{Min}	F28
τ	F10	$SBP_{Max-Min}$	F29
m	F11	SBP_{Mean}	F30
CD	F12	SBP_{svMax}	F31
α_1	F13	SBP_{SD}	F32
α_2	F14	DBP_{Max}	F33
L_{Mean}	F15	DBP_{Min}	F34
RT	F16	$DBP_{Max-Min}$	F35
V_{Max}	F17	DBP_{Mean}	F36
TT	F18	DBP_{svMax}	F37
L_{Max}	F19	DBP_{SD}	F38

3.2. Feature Selection

One of the most important processes to improve the performance of death class classification systems is the selection of features that can have the most information from the output class. Reducing the dimension of the feature space reduces the complexity of the classification process and thereby reduces the occurrence of the error. The problem of feature selection is one of the issues raised in the discussion of machine learning as well as the statistical identification of the model. This is very important in many applications, such as classification, because there is a large number of features in these applications, many of which are either unused or having little information load. Not-eliminating these features do not create a problem in terms of information but raise the computational load for the intended application. Moreover, it causes a lot of non-useful information, along with useful data, to be stored.

3.3. Mutual Information (MI)

One of the proposed approaches to select the feature space is the mutual information method. The main objective of using this procedure is to produce features that have the minimum mutual information while simultaneously enjoy the maximum mutual information with the output class. In this paper, this method is used to predict the death class of cerebral ischemic patients in the ICU.

Swinney and Fraser presented the mutual information as a means to determine the time delay. Before proposing this approach, the autocorrelation function method was used to determine the time delay. But the problem with the autocorrelation function method was that this method only considered linear correlations [49]. Unlike the autocorrelation function, the mutual information also considers the non-linear correlations in the time series. The mutual information for different values is calculated from equation (3).

$$M(\tau) = - \sum_{i,j} p_{ij}(\tau) \ln \frac{p_{ij}(\tau)}{p_i p_j} \quad (3)$$

In the above equation, p_i is the probability of finding a time series value in i distance, and $p_{ij}(\tau)$ is the joint probability that observation occurs at i^{th} distance, and the next observation occurs with delay τ at j -th distance. Finally, the first minimum of the M function in terms of τ is considered as the optimal delay value.

The ten features that were placed in higher ranks in this method and contained more information regarding the death class with two, three combinations were determined, and finally, ten of the top features were evaluated by the thresholding algorithm. In the thresholding algorithm to calculate the threshold value for determining the death class and non-death class, the value of each feature is calculated within a half-hour interval, and then the ratio of the two features in two successive intervals is determined. The threshold value of each feature for the death class is the average ratio of the interval 0.5-0.1 hours to 1-1.5 hours before death.

3.4. K-fold cross-validation

Once the model is developed, it is used to predict the mortality of cerebrovascular patients. Therefore, model evaluation and validation is a very important process. Cross-validation is a statistical method for evaluating and comparing learning algorithms that divide data into two distinct parts: One section is used to learn or train the model, and the other is used to evaluate the model.

K-fold cross-validation is one of the popular methods of model evaluation. In this method, the data is randomly divided into k separate subset, and k times the training and evaluation are performed. In this way, each time one of the subsets is kept to evaluate the model, and the other $k-1$ subset is used to train the model. This process is repeated k times; So that each subset is used exactly once to evaluate the model. Finally, the result of this k iteration is averaged to achieve a final estimate. In this way, all the data will be present in both the

training and evaluation groups, and therefore, the evaluation method has been considered more accurately. In general, a 5-fold cross-validation process is proposed to estimate the performance of the proposed model.

Then, using a 5-fold cross-validation method, the training data were randomly divided into 5 separate subsets. In this way, one of the subsets is considered for model evaluation, and the other 5 subsets are considered for the training model. Then, the model is trained using the 5 subsets considered, and another residual subset is used to predict the behavior of the model and evaluate it. This process uses criteria of the accuracy, specificity, and sensitivity to determine the predictive performance of the model. This process is repeated 5 times; So that each of the subsets is selected exactly once to evaluate the model, and to use the criteria mentioned above, evaluates the predictive performance of the model. After that, the average result of these 5 iterations is calculated. The averaged value indicates the final predictive performance of the model based on the 5-fold cross-validation method.

In this paper, 75% of the data (66 people) were used for training, and the remaining 25% (22 people) were used for testing the death and non-death class prediction system. For all prediction tests, estimates of the accuracy, sensitivity, and specificity is reported with 0.95 confidence intervals (CIs).

A comparison of the classification function of the death and non-death class for cerebral ischemia, using superior features, has been represented in Table 3 and Figure 5. As shown in this Table, the combination of the five top features could have a better performance in predicting the death class than the other combinations.

Table 3. Comparison of classification performance of death and non-death classes using the superior features obtained from the mutual information method

Number of features	Top Selected Features	Accuracy (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)
3	F22,F35,F31	71.2% (53.5-79.2)	75.4% (56.3-80.2)	71.1% (52.7-79.5)
4	F22,F35,F31,F10	80.3% (60.8-86.6)	83.3% (61.3-87.8)	79.5% (54.3-85.2)
5	F22,F35,F31,F10,F15	87.9% (72.1-92.7)	88.6% (74.3-94.5)	84.8% (68.2-90.6)
6	F22,F35,F31,F10,F15,F26	83.3% (64.4-88.1)	86.2% (66.2-89.4)	81.6% (61.3-85.7)
7	F22,F35,F31,F10,F15,F26,F11	85.6% (62.9-90.2)	85.8% (63.5-89.4)	81.2% (62.4-86.3)
8	F22,F35,F31,F10,F15,F26,F11,F21	80.7% (58.7-88.3)	83.7% (63.4-89.2)	78.5% (57.6-84.3)
9	F22,F35,F31,F10,F15,F26,F11,F21,F20	80.1% (58.5-86.7)	83.4% (61.6-88.6)	78.1% (56.8-83.9)
10	F22,F35,F31,F10,F15,F26,F11,F21,F20,F6	77.3% (54.9-83.4)	80.2% (59.5-84.7)	74.6% (53.2-79.7)

3.4. Genetic Algorithm (GA)

A variety of methods have been proposed for feature selection so that a proper subset of the features among the feature set is achieved. The Genetic Algorithm (GA) is one of the most powerful evolutionary algorithms used in the feature selection stage and as a classifier in various studies. In this algorithm, we generate a population of the candidate subsets. In each iteration of the algorithm, we produce new elements using the mutation and crossover operators on the elements of the previous population. Using an evaluation function, we identify the fitness function of the current population elements and select the better elements as the next generation population. Finding the best solution in this approach cannot be guaranteed, but it always finds a good solution to the length of time allowed to run the algorithm. Figure 6 shows the block diagram of the procedure of implementing the genetic

algorithm. A comparison of the classification function of the death and non-death class using the superior features obtained from the genetic algorithm for patients with cerebral ischemia is shown in Table 4. The highest accuracy, specificity, and sensitivity of the proposed system in this paper using the five top features were calculated to be 87.9%, 88.6%, and 84.8%, respectively. Also, the positive predictive ratio (PPV) and the negative predictive ratio (NPV) for the best combination was reported 92.35% and 88.21%, respectively. Figure 7 indicates the result of the proposed system with the help of various superior features (3 to 10).

Table 4. Comparison of classification performance of death and non-death classes using the superior features obtained from the genetic algorithm

Number of features	Top Selected Features	Accuracy (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)
3	F35,F31,F22	74.1% (60.3-81.6)	79.3% (63.1-84.6)	73.2% (59.3-80.9)
4	F35,F31,F22,F29	83.2% (65.8-89.6)	87.4% (68.2-93.2)	82.9% (64.5-88.5)
5	F35,F31,F22,F29,F10	90.2% (74.3-94.7)	92.1% (76.5-97.1)	89.9% (73.8-93.1)
6	F35,F31,F22,F29,F10,F15	87.3% (72.1-94.2)	88.1% (73.1-93.8)	86.5% (71.4-92.8)
7	F35,F31,F22,F29,F10,F15,F38	87% (73.4-92.6)	88.3% (74.5-93.4)	85.1% (73.1-91.1)
8	F35,F31,F22,F29,F10,F15,F38,F19	85.9% (72.5-91.8)	87.8% (73.7-92.7)	83.8% (71.7-90.4)
9	F35,F31,F22,F29,F10,F15,F38,F19,F9	85.2% (70.2-90.3)	87.2% (72.3-91.4)	83.3% (69.2-89.6)
10	F35,F31,F22,F29,F10,F15,F38,F19,F9,F6	82.7% (67.5-89.1)	83.5% (68.2-90.7)	81.4% (66.5-87.6)

3.5. The combinations of feature to determine the death or non-death class

Then, because the combination of information with a high degree of importance can weaken the performance of the prediction system, the search for the best combination of all the existing combinations of this feature set was addressed. Finally, the results of using the two listed methods were compared. Taking into account that the top ten features were selected using mutual information, there will be different two, three, and eventually, ten combinations, which are represented in Tables 3 and 4. Table 5 and Figure 8 show the comparison of classifier performance of the death and non-death class for the cerebral ischemia using the best combination of features. As can be seen in this Table, the best combination of features among a set with ten features that have better differentiation than other features is related to the combination of different five-feature by the combination of superior features. The five features obtained from the mutual information include F35, F31, F22, F29, F10, while the best five-feature combination, F11, F15, F22, F31, F35, was introduced. Table 6 and Figure 9 show the best combination of features obtained from the genetic algorithm. The comparison of results obtained from the methods of mutual information and genetic algorithm demonstrates that the use of the genetic algorithm leads to the selection of more efficient features. Using the best combination of features obtained from the genetic algorithm, the proposed system could achieve accuracy, specificity, and sensitivity of 97.7%, 98.9%, and 95.4%, respectively. Also, the PPV and the NPV for the best combination was reported 99.3% and 97.4%, respectively.

Table 5. Comparison of classifier performance of death and non-death classes using the best feature combination obtained from the mutual information method

Number	Number of	Best Feature Combination	Accuracy	Specificity	Sensitivity

of features	possible combinations		(95% CI)	(95% CI)	(95% CI)
3	120	F15,F22,F35	73.5% (54.2-79.5)	75.2% (56.7-80.3)	72.7% (53.5-78.1)
4	210	F10,F22,F31,F35	80.1% (62.3-86.1)	82.7% (64.4-88.6)	79.5% (60.3-85.2)
5	252	F11,F15,F22,F31,F35	91.5% (75.2-95.1)	92.1% (77.4-97.5)	89.6% (74.8-95)
6	210	F11,F15,F21,F26,F31,F35	85.8% (67.1-90.9)	86.5% (70.4-93.3)	83.1% (76.2-90.1)
7	120	F6,F10,F15,F20,F22,F31,F35	83.9% (65.2-87.7)	85.3% (68.4-92.7)	80.8% (64.6-86.7)
8	45	F10,F11,F15,F21,F122,F26,F31,F35	83.2% (63.2-87.9)	84.6% (65.3-90.4)	82.2% (63.1-87)
9	10	F6,F10,F15,F20,F21,F21,F26,F31,F35	82.6% (63.1-87.2)	83.9% (64.6-89.7)	80.4% (61.2-86.5)
10	1	F6,F10,F11,F15,F20,F21,F22,F26,F31,F35	79.7% (62.4-85.4)	81.4% (63.3-89.1)	78.5% (60.2-84.2)

Table 6. Comparison of classifier performance of death and non-death classes using the best feature combination obtained from the genetic algorithm

Number of features	Number of possible combinations	Best Feature Combination	Accuracy (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)
3	120	F15,F22,F35	81.6% (63.2-88.7)	83.4% (67.5-90.2)	80.2% (61.5-87.3)
4	210	F10,F22,F31,F35	88.2% (70.1-93.5)	90.5% (71.3-97.3)	87.4% (68.2-91.5)
5	252	F11,F15,F22,F31,F35	97.7% (80.2-100)	98.9% (81.4-100)	95.4% (79.3-100)
6	210	F11,F15,F21,F26,F31,F35	92.3% (77.1-98.4)	93.6% (79.4-99.3)	91.3% (75.2-96.8)
7	120	F6,F10,F15,F20,F22,F31,F35	91.2% (75.6-97.8)	92 % (78.1-98.8)	90.8% (73.2-96.7)
8	45	F10,F11,F15,F21,F122,F26,F31,F35	89.21% (74.1-97.3)	90.1% (76.5-97.9)	88.4% (72.4-95)
9	10	F6,F10,F15,F20,F21,F21,F26,F31,F35	88.3% (72.4-95.7)	89.6% (74.2-96.1)	86.8% (70.1-93.5)
10	1	F6,F10,F11,F15,F20,F21,F22,F26,F31,F35	85.6% (68.8-93.2)	87.3% (70.2-94.7)	84.6% (66.4-91.6)

In the healthcare field, where prediction models are often developed on patients with different conditions, the uncertainty determining of the prediction models could potentially lead to improved effectiveness of decision-making systems and increased nursing and physician trust.

The main purpose of this paper is to investigate the physiological parameters of cerebrovascular patients to predict their mortality in the future. These predictions are subject to uncertainty because the algorithm used for modeling differs from what actually exists. Even due to the uncertainty in the information and inputs of the model, the final result may be affected. Therefore, assessing and computing the uncertainty in presenting the prediction model could play an important role in the validity of the proposed model. In this paper, the Monte Carlo method is used to estimate the uncertainty of the model output. In this method, the parameters (inputs to the model) are randomly selected using the probabilistic distribution function, and then their corresponding output is obtained from the model, and this method is repeated many times. In the next step, the output uncertainty

(model) is satisfied by computing statistical parameters or determining the probability distribution function [51].

To determine the uncertainty, the 95 percent prediction uncertainty (95PPU) is considered, so that it is about 2.5% (X_L) and 97.5% (X_U) of the cumulative probabilistic probability distribution obtained from the many predictions.

Appropriate prediction confidence is the ranges that more than 90% of the observed values are within and have an acceptable average width. The average bandwidth factor is calculated by equation (4).

$$d - factor = \frac{\overline{d_x}}{\sigma_x} \quad (4)$$

Where σ_x is the observed standard deviation and $\overline{d_x}$ is the average distance between the upper and the lower 95PPU (or the degree of uncertainty) determined as equation (5).

$$\overline{d_x} = \frac{1}{n} \sum_{i=1}^k (X_U - X_L)_i \quad (5)$$

Where k is the number of observed data points, the value of less than 1 is a desirable measure for the d-factor. The 95 percent prediction uncertainty (95PPU) is as the equation (6).

$$Bracketed \text{ by } 95PPU = \frac{1}{n} count(Q | (X_L < Q < X_U)) \times 100 \quad (6)$$

The desired 95PPU value is 100% [52]. Table 6 shows the uncertainty parameters of the prediction models.

Table 6. The results of uncertainty parameters for different prediction models

Uncertainty parameter	Superior Features-MI	Superior Features-GA	Best Feature Combination-MI	Best Feature Combination-GA
d-factor	1.69	0.93	0.89	0.95
Bracketed by 95PPU (%)	84.2	94.3	97.5	98.6

As shown in Table 6, the uncertainties in most prediction models except the superior features-MI model are optimal, and the amount of uncertainty is low. The amount of d-factor in the superior features-GA model, the best feature combination-MI model, and the best feature combination-GA model is less than 1. At the same time, this value is greater than 1 in the superior features-MI model. These results show proposed models have optimum uncertainty in mortality prediction of the cerebrovascular patients.

4. Discussion

In this paper, the mortality prediction of cerebral ischemic patients in the ICU using different methods and employing different characteristics of HRV signal and blood pressure was examined. To better and more accurately predict the mortality of patients with cerebral ischemia, features extracted from blood pressure and new features extracted from the return map generated from the HRV signal were used. Initially, based on the behavioral change in the HRV signal and blood pressure in half-hour intervals, valuable time intervals and features that had a better differentiation between the risk of death and non-death intervals were selected and used them to predict the mortality. Then, according to the selected features, using the selection of optimal threshold and it changes, and calculation of the accuracy, specificity, sensitivity, prediction horizon, and length of stay of patients for each of the features, the mortality prediction system proposed in this paper was evaluated.

As previously mentioned, the features that initially had a good differentiation using the T-test statistical analysis to identify the patient's entry to the death interval were selected, and each of these features was evaluated independently and reported according to the accuracy, sensitivity, and specificity of the obtained features. To combine these features, the features that have exhibited the best response in relation to the level of accuracy, sensitivity, and specificity were used. But it is important to note that these features may have shared information and ultimately negatively affect the performance of the performance system.

Thus, in order to combine these features, we first used features selection methods such as mutual information and genetic algorithm. Then, the selected features were employed, and the results of using various combinations to calculate the acceptable level of accuracy, sensitivity, and specificity were reported.

The results indicated that, of the different methods outlined in this paper, the new features extracted from the return map were more capable of achieving the higher level of accuracy, specificity, sensitivity, and forecast-horizon and lower length of stay for implementing the prediction system on patients with cerebral ischemia. According to the obtained results based on different features, the combined use of features for better prediction was ultimately evaluated. The proposed combination feature increased the prediction of the risk of death interval, while the ability of the prediction system to determine intervals in which death does not occur increased and the false prediction rate also declined. In this paper, given that systolic and diastolic blood pressure was also a risk factor for mortality in ischemic patients, this feature was also added to the features extracted from heart rate and improved the performance of the prediction system in determining the death interval and reducing the prediction error rate.

Finally, to systematize the patient mortality prediction process, a genetic algorithm (GA) and mutual information (MI) was used for feature selection. Using the selected features by this method and finding the optimal combination to increase the performance, the results were reported.

In this article, to enhance the performance of the proposed system in predicting the mortality of patients with cerebral ischemia, after extracting the various features of heart rate and blood pressure, the feature selection by the methods of mutual information and genetic algorithm and their combination was addressed. Figure 10 shows the accuracy obtained from different methods of selection and the combination of features in the proposed system. As can be seen in this Figure, the use of five superior features of genetic algorithms and then the best possible combination of these features has the highest level of accuracy. Figures 11 and 12 show the level of sensitivity and specificity of the proposed system with different features. As shown in these Figures, when very low or very high features are used, the system does not have a high potential in the prediction of death interval.

Finally, the use of the genetic algorithm for feature selection forecast horizon of 0.5-1 hour before death could predict the mortality of patients with cerebral ischemia with accuracy, specificity, and sensitivity of 97.7%, 98.9%, 95.4%, respectively. According to the results gained, using the combination of superior features selected by the genetic algorithm in the training and testing phase, the system with the forecast horizon of half-hour before death will issue a false alarm of death at 1.64 times and 1.95 times, respectively, during a day.

Research has been conducted on the mortality prediction of patients with cerebral ischemia using medical software and vital signal processing. BH et al. carried out a study on the mortality prediction in 469 patients with cerebral ischemia from 2011 to 2012 using APACHE and SAPS software. The mortality rate observed in these patients was 26.3%, while this software predicted mortality of these patients to be 35.12% and 35.34%, respectively. Raj R et al. performed a study on the mortality in 1625 patients with brain damage during the six months with the help of APACHE, SAPS, and SOFA software, and was able to predict the death of these patients by 82%, 83%, and 72%, respectively. Henian Xia et al. used the neural network to predict the mortality, with the difference that they benefited from other physiological parameters as well. The mortality prediction rate obtained in this study was 82.21%. Srinivasan V et al., using a hidden Markov model, could predict the mortality up to 78.90%. It should be noted that the number of parameters employed in this study was 27. De Simone G et al., in research on 5380 cerebrovascular patients, found that systolic and diastolic blood pressure plays an important and key role in the mortality

prediction of these patients. Comparing the results of various studies in this field with the results of this paper indicates the presence of valuable information in the return map of HRV signal and systolic and diastolic blood pressure in order to predict the mortality of patients with cerebral ischemia better.

5. Conclusion

The results of investigations carried out by authors of this article on the mortality of cardiovascular and cerebrovascular patients in several recent years show that the HRV of these patients in near-death intervals compared to far-death intervals is different. Biological systems exhibit non-linear behavior. Thus the use of non-linear features can better illustrate the realities of the system at different times as well as, and the return maps can reveal the hidden structures in the signal due to the analysis of biological signal changes in the heart rate. The examination of blood pressure and heart rate provided valuable information about the prediction of the patient's future status and could prolong the forecast horizon. By illustrating the difference in variations at the near and far away from death, biological signals are known as risk factors for mortality of cardiovascular and cerebrovascular patients.

Abbreviation

DBPMax : Maximum diastolic blood pressure

DBPMax-Min : maximum-minimum difference in diastolic blood pressure

DBPMean : mean diastolic blood pressure

DBPMin : minimum diastolic blood pressure

ECG: Electrocardiography

FPR: False positive rate

FNN: False nearest neighbor

GCS: Glasgow Coma Scale

GFI: goodness of fit index

HF: High frequency

HRV: Heart rate variability

ICU: Intensive Care Unit

KMT: Kolmogorov-Smirnov test

LOS: length of stay

LF: Low frequency

MI: Mutual information

NPV: Negative predictive ratio

PPV: Positive predictive ratio

RMSSD: Root Mean Square of the Successive Differences

SBPMax : Maximum systolic blood pressure

SBPMax-Min : maximum-minimum (differences) in systolic blood pressure

SBPMean : Mean systolic blood pressure

SBPMin : minimum systolic blood pressure

SBPSVMax : maximum of the average squared difference between successive measurements for systolic blood pressure

SD1: Standard deviations one

SD2: Standard deviations two

SDANN: Standard deviation of the mean of sinus R-R intervals

SDNN: Standard deviation of the NN intervals

VLF: Very low frequency

Ethics approval and consent to participate

The institutional review board (IRB) of the Canton of Bern approved the study. The need for obtaining informed patient consent was waived owing to the retrospective and observational nature of the study.

Consent for publication

Not applicable.

Availability of data and material

Not applicable.

Competing interests

Authors have no conflict of interest to declare

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Authors' contributions

MKM, SKS, AMN, and EH conceived the study, designed the trial, and obtained funding. MKM managed the data, including quality control. AMN and EH provided statistical advice on study design and analyzed the data. MKM drafted the manuscript, and all authors contributed substantially to its revision. All authors have seen and approved the final draft for submission.

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Figures

Figure 1

The most important parameters of an ECG signal

Figure 2

Predictive criteria for mortality on heart rate variability signal

Figure 3

Changes in the values of extractable features of blood pressure and heart rate in different time intervals

Figure 4

Comparison of the specificity and sensitivity for the predictive system of death in patients with cerebral ischemia

Figure 5

Comparison of the performance of the proposed system using the superior features obtained from the mutual information method

Figure 6

A block diagram of the genetic algorithm

Figure 7

Comparison of the performance of the proposed system using the superior features obtained from the genetic algorithm

Figure 8

Comparison of the performance of the proposed system using the best combination of features obtained from the mutual information method

Figure 9

Comparison of the performance of the proposed system using the best combination of features obtained from the genetic algorithm

Figure 10

Accuracy of the proposed system by using superior methods and different feature combinations

Figure 11

Specificity of the proposed system by using superior methods and different feature combinations

Figure 12

Sensitivity of the proposed system by using superior methods and different feature combinations