



Predicting the Risk of Diabetes in Iranian Patients with β -Thalassemia Major / Intermedia Based on Artificial Neural Network

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Abstract

The purpose of this study is to predict catching diabetes in patients having the β -thalassemia. Here, an intelligent system predicts risk of catching diabetes in patients having major thalassemia and intermedia, using multilayer perceptron according to the thalassemia dataset, ZAFAR. In this work, the clinical characteristics of 255 patients, having β -thalassemia, have been studied in two groups of diabetic and non-diabetic patients. Research data includes gender, age, parental family relationship, type of thalassemia, the spleen, gall bladder and liver condition, the age of blood transfusion, blood transfusion intervals, the number of received blood units in each period, the condition of iron overload, the age of start iron chelation therapy, the average of heart T2 rates, the liver T2 and LIC, the number of years having MRI, serum ferritin level, glucose and the number of years the patient was observe. The accuracy of artificial neural network in diagnosing the patients having thalassemia and exposing diabetes would be 80.78% according to the collected dataset. The accuracy rate of the system is 89.48%, using this intelligent system and doing pre-processing. This system has a desirable performance in predicting catching diabetes in patients having β -thalassemia. The best mean square error in this model is 0.07 which results in reducing learning time and increasing the system accuracy. Based on the obtained results from this system, there are two important factors in catching diabetes by the patients having β -thalassemia; first the number of years passed by patient with the high serum ferritin level and second is the glucose level rate in previous years long.

Keywords: β -thalassemia, Diabetes, Artificial Neural Network, Multi-Layer Perceptron.

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1. INTRODUCTION

Thalassemia was first discovered by a scientist named Cooley in 1925. Therefore, it is called Anemia- Cooley. Today, this disease has been reported all over the world due to people's migration. However, the disease spreading is more in Mediterranean countries, the equator, and its vicinity. Thalassemia ranges are more wide spreading in Mediterranean coast, throughout Saudi Arabian, Turkey, Iran, India and Southeast Asia, especially Thailand, Cambodia and South China [1]. B-thalassemia is the most common form of hemolytic anemia and about 60000 babies having thalassemia are born throughout the world each year that are controlled and looked after by blood transfusion, and iron chelation therapy [2]. Thalassemia is a genetic disorder disease that loses its natural structure hemoglobin and body produces impractical hemoglobin that consists of two kinds which are Alfa and Beta. The Alfa type of this disease is a hidden one and it is also called the Minor β -thalassemia. B-thalassemia itself consists of two kinds which are Major (severe) and Intermedia. The term β -thalassemia intermedia refers to the patients having more severe clinical symptoms in comparison with Minor thalassemia that is a less severe type of Major thalassemia [3] in which a patient doesn't need to be injected blood regularly. The gathering of iron in body and the lack of its excretion result in producing siderosis in different tissues and organs that result in cells death and fibrosis and disabling the involved organs [4]. Among all involved organs, the heart, liver and endocrine suffer the most in which the most important problems of siderosis in excretive glands consist: stature shortness, growth failure, delayed puberty, hypothyroidism, hyperparathyroidism,

mellitus diabetes, abnormalities in glucose metabolism, reducing cortisone level [5]. Among all the above disorders, mellitus diabetes makes the most injuries on patients due to its own harmfulness's. According to the conducted studies by Dr. Azarkeivan et.al on 437 patients having major thalassemia and intermedia in two groups of diabetic and non-diabetic disease, the blood transfusion unit has a remarkable difference in diabetic and non-diabetic patients. This result shows the negative effects of blood transfusions in these patients and consequently the increase of iron overload in body [6]. The health of people in society is based on the results of medical researches that have a high effect on all the body activities. On the other hand, in medical sciences, a good interpretation of data is so crucial at the early diagnosis. This issue could be considered as the basis of a nice and effective treatment, especially in hematology and other medical fields [7]. Decision making in medicine is considered as a very hard activity since the analysis carries a huge amount of data and doctors mostly suffer the lack of having the accurate analysis of laboratory data, therefore they need a tool to decide accurately. In recent years, expert systems and artificial intelligence techniques have helped doctors decide better and have more effective performances in this field [8]. Recently, common researches have been done in the field of artificial intelligence and medical science such as: the application of neural network to predict the survival of patients having the gastric cancer [9] and using techniques such as fuzzy classification based on ant colony algorithm [10]; as well as the intelligent hybrid system composed of fuzzy neural network, the regression tree and random forest [11]; intelligent system based on linear discriminant analysis and fuzzy

inference systems-based adaptive network [12]; the decision tree [13]; hybrid model of neural networks and genetic algorithms [14]; Support Vector Machine (SVM) [15]; and Bayesian network [16]; which are used to diagnose and predict diabetes. KNN¹, SVM, MLP² and DT³ have been used to predict and diagnose Alpha and β -thalassemia [17-19], prediction of mellitus diabetes in patients with Beta- thalassemia using RBF⁴ and KNN is also performed [20].

Multi-layers perceptron which is one of the most popular tools in classifying the artificial intelligence is so much useful in medical fields to predict and diagnose diseases, the performance of surgery and other medical procedures [21-23]. The structure is based on the recognizing of human brain function. Here, some applications have first been used to enhance the network function on data collection and then the multi-layers perceptron will be used to predict the diabetes in patients having thalassemia. By predicting diabetes in the patients having thalassemia, the procedure of patients' treatment and frequent pursuing to treat can be affected. On the other hand, by having the on-time treatment to reduce ferritin, the patient will be kept immune to catch other diseases due to the siderosis.

In attachment of the essay in the second part, the collected dataset from Zafar Adult Thalassemia center of Tehran will be discussed. In the third part, the artificial neural network will be discussed and its results will also be presented. Then, in the fourth section, the proposal will be discussed in details and the output of neural network will be presented considering the proposal. In the final section,

the possible methods will be evaluated and the possible achievements from the studies will be presented.

2. THALASSEMIA DATASET

This study was conducted based on paraclinical data obtained from the 1575 files of patients with thalassemia having referred to Zafar Adult Thalassemia Clinic in Tehran. From 1575 patients with thalassemia, there were 255 cases with complete clinical features (demographic data, genetic testing, hematology, biochemistry of bone densitometry testing, abdominal ultrasound, heart and liver MRI) that all the information related to each patient were recorded.

Among these data, the values of parameters like gender (female = 1 and male = 0), age, parental family relation (positive = 1 and negative = 0), type of thalassemia (major = 1 and intermedia = 0), spleen condition (normal spleen size = 0 and more than normal size = 0.5 and asplenia (Splenectomy) = 1), gallbladder (normal = 0, the presence of stones in the bile = 0.5 and absence of the gallbladder = 1), liver (normal = 0, parenchyma = 0.5), onset of blood transfusion, blood transfusion intervals, the number of received blood units in each period, the age of start iron chelation therapy, the mean of heart T2 (descriptive values, normal = 0, mild = 0.3, moderate = 0.6 and severe = 1), the mean of liver T2 MRI (descriptive values, normal = 0, mild = 0.3, moderate = 0.6 and severe = 1), number of years of controlling MRI, mean of serum ferritin level, glucose and the number of years in which the patient was under observation were selected to

¹ K-Near Neighbor

² Multi-Layer Perceptron

³ Decision Tree

⁴ Radial Basis Function

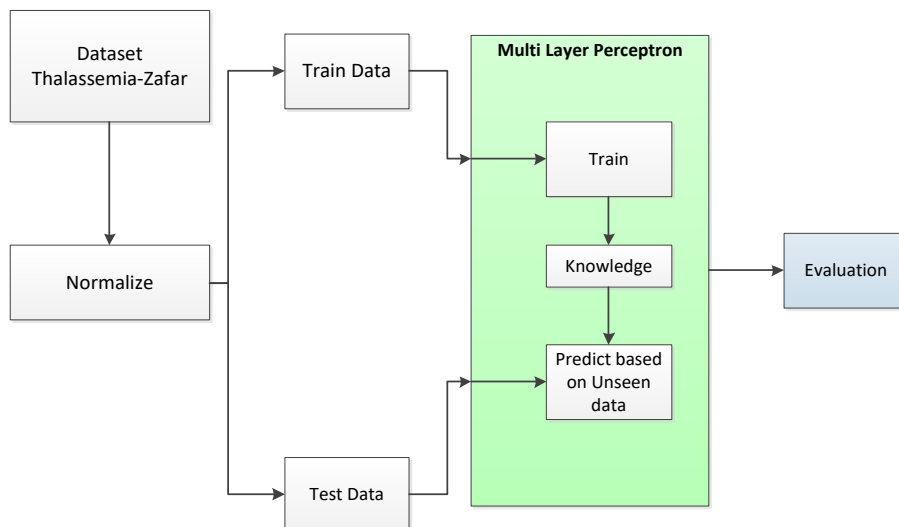


Fig. 1. The workflow of intelligent system.

predict diabetes. This data has been divided into two groups of thalassemia patients with diabetes and non-diabetes. 80 persons are in diabetes group and 181 are non-diabetes one.

3. ARTIFICIAL INTELLIGENCE NEURAL NETWORK

In this work, a three-layer perceptron has been used to predict the risk of catching diabetes. This MLP consists of four stages. In the figure 1, the workflow of this system is observed.

The workflow of this intelligent system is discussed below.

Step 1. Input: Zafar thalassemia dataset is entered to system as input.

Step 2. Standardization: All the nominal and descriptive values of the dataset are changed to numerical values and next the training data and test data will be separated. From 255 available samples in the dataset, 56 records of each class of training dataset and 149 reminded records make the test dataset. The performance of the network is evaluated based on 149 unseen data.

Step 3. Learning based on Multilayer Perceptron: There are different ways of learning in the artificial intelligence field. Learning method selection is based on the type of dataset and the problem scope. Multilayer perceptron is one of the most widely used techniques in the learning field in classification due to the tolerance and high performance [24]. In this dataset, this method was used due to the lack of having knowledge of hereditary diabetes in the patient. As we know, hereditary diabetes is effective on its catching. Therefore, the cause of diabetes in patients with thalassemia maybe the inheritance of diabetes, not fibrosis. Thus, the multilayer perceptron was used due to the tolerance of errors. The network consists of an input layer, a middle layer and an output layer. The number of neurons in the input and output layer is based on the dataset. Finding the best neuron numbers in the middle layer is based on the trial and error. Data values include gender, age, parental family relationships, type of thalassemia, the spleen, gall bladder and liver condition, age of blood transfusion,

blood transfusion intervals, the number of received blood units in each period, The condition of iron overload, the age of iron chelation therapy, the mean of heart and liver T2* MRI and LIC, the number of years for control of MRI, the serum ferritin level, glucose and the number of years the patient was under observe, which are entered in the input layer of network.

The number of neurons in the input layer is based on the number of this data which are 17 here. The number of neurons in the first middle layer is 50 and in the second middle layer is 65 and sigmoid activation function was used in middle and output layer. The number of dataset classes determines the number of neurons in the output layer. In this dataset, we have two classes of diabetic and non-diabetic group, so we will have two neurons in the output layer. The best learning rate in this network based on conducted tests is 0.008. The stop condition is based on the mean square error the most suitable value is 0.07 for the mean square error.

Step 4. Evaluation: Commonly, three parameters are used to determine the performance of classification algorithms. These metrics show the accuracy rate of each method classification and are also considered as index to compare algorithms. The evaluation indexes consist of sensitivity rate, specification rate and accuracy rate. First, the effective parameters in calculating the evaluation criteria will be discussed and next the method of its calculation will be stated.

True Negative (TN): includes the number of samples which do not belong to the considered class and was considered correct by the network.

True Positive (TP): includes the number of samples which belong to the considered class

and was also considered correct by the network.

False Negative (FN): includes the number of samples which do not belong to the considered class and was considered for this class by the network.

False Positive (FP): includes the number of samples which belong to the considered class and was classified by the network for other class.

Based on the achieved amounts from the above sensitivity, specification and accuracy rate are calculated.

The rate of recall or sensitivity show the true positive (TP) rate predicted positive in the class correctly. According to this index, it can be understood that how much the considering method is able to diagnose the related patterns in each class, which is achieved from the equation (1) [25].

$$\text{Recall} = \frac{\text{TP}}{\text{TP} + \text{FN}} \quad (1)$$

Precision is the inverse of the recall. This parameter shows the ratio of the cases predicted in the positive class to the true positive cases, which is calculated by using the equation 2.

$$\text{Precision} = \frac{\text{TP}}{\text{TP} + \text{FP}} \quad (2)$$

The learning performance can be shown by using the accuracy rate index. Commonly, this index is used to compare different classification methods which are achieved by considering the equation 3.

$$\text{Accuracy} = \frac{\text{TN} + \text{TP}}{\text{TN} + \text{FN} + \text{TP} + \text{FP}} \quad (3)$$

It should be mentioned that the above amounts are calculated per each class. Here, due to the double class, the rate of achieved

accuracy in each class will be the same. In this stage, the system performance is evaluated based on the test (unseen) dataset.

4. FEATURE EXTRACTION

As mentioned in the introduction part, the excretive glands disorder is one of the problems of iron aggregation in body that results in risk of catching diabetes. Consequently, the rates of “glucose” and “serum ferritin level” are the effective factors in catching diabetes in the patients having thalassemia. On the other hand, the number of years that this amount of serum ferritin level has deposited in the body is important because the body will suffer more damage over time. Therefore, in this study, the average serum ferritin level is calculated based on the available information in the file and then is multiplied by the years the patient was under observation, so this pre-processing results in the better recognition of the patients

endangered with the disease. The glucose is the fundamental parameter to predict catching the diabetes. With the accumulation of serum ferritin level and time passing, the amount of glucose in blood will gradually be increased, which indicates the pancreatic disorder in which the patient will eventually catch diabetes. So, the mean of glucose is calculated based on the available information, and next is multiplied by the years the patient was under observation. One of the important steps that has been done to improve the performance of the network is the calculation of the difference in blood glucose in patients with the normal size (the normal range of blood glucose has been considered 110). By helping this feature, the network can distinguish the patients having the lower blood glucose level with the ones having the higher level of normal. In figure 2, the system of working procedure method is shown by the pre-processing function. In total, the feature "the number of years the patient was under observation" has

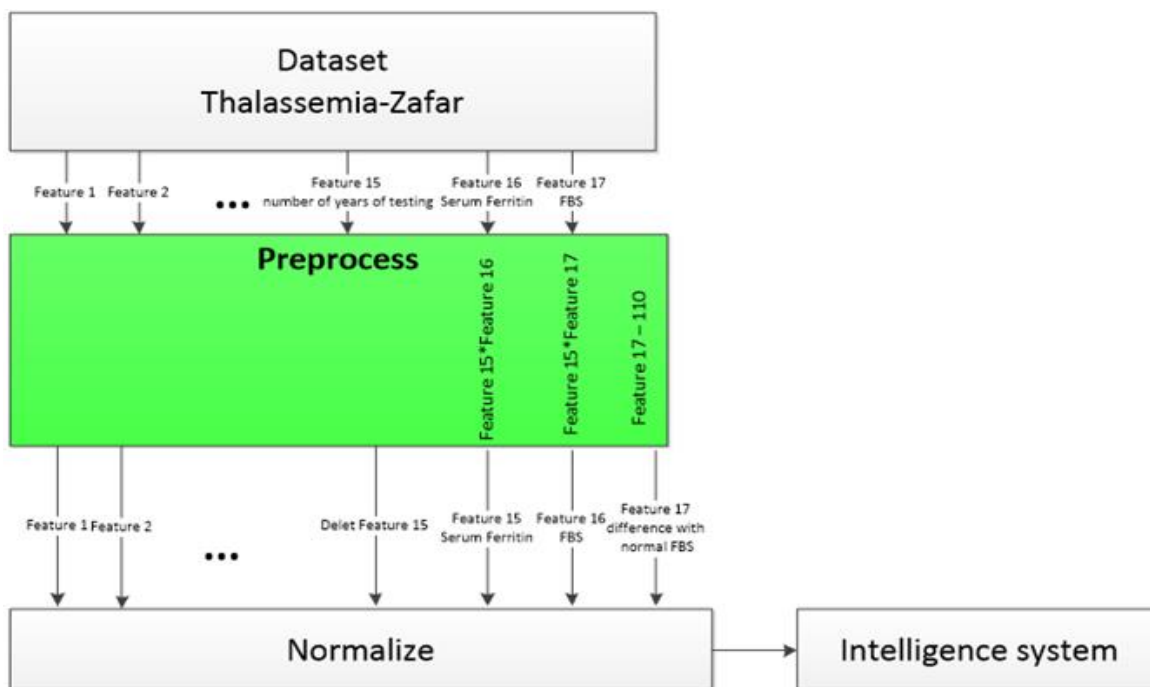


Fig. 2. Proposed model of intelligent system.

Table 1. Frequency type of β -thalassemia in each class.

Classes	Number	Percent	Type β -thalassemia	Number	Percent
Diabetes	74	29%	Intermedia	15	20.27%
			Major	59	79.73%
None-diabetes	181	71%	Intermedia	64	35.36%
			Major	117	65.64%
Total	255	100%		255	

been removed from the dataset, and the features values "serum ferritin level" and "glucose" were edited and the "different rate of blood glucose with the normal rate" was added to the dataset.

5. RESULTS

The study population consisted of 255 patients with β -thalassemia, 74(29%) patients with thalassemia had the diabetes and 181(71%) patients with thalassemia had not the diabetes. Totally, 79(31%) patients had the thalassemia intermedia and 176(69%) patients had the thalassemia major. About thalassemia patients with the diabetes, 15(20.27%) patients were thalassemia intermedia and 59(79.73%)

patients were thalassemia major, but about thalassemia patients without diabetes, 64(35.34%) patients were thalassemia intermedia and 117(65.64%) patients were thalassemia major. (Table 1 and figure 3) The multilayer perceptron with 17 input nodes, 50 nodes in the first hidden layer, 65 nodes in the second hidden layer and 2 nodes in the output layer and sigmoid activation function in hidden layers and output layer was trained. Training dataset includes 102 record (51 randomly samples were selected from each class for training data) and the testing (unseen) dataset is 153 record (23 samples from diabetic class and 130 samples from none-diabetic class were selected).

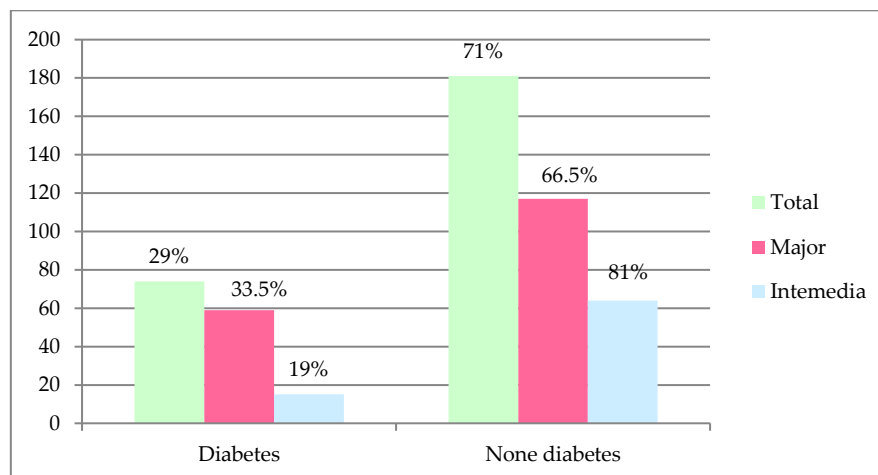
**Fig. 3. Frequency type of β -thalassemia in each class.**

Table 2. Results from MLP neural network.

Mean Square Error	The number of repetitions in stopping time	Recall None-Diabetes	Precision None-Diabetes	Recall Diabetes	Precision Diabetes	Accuracy
0.07	896	81.08%	95.63%	79.13%	44.03%	80.78%
0.01	3758	60%	94.93%	83.3%	28.57%	63.75%
0.08	695	69.60%	73.15%	91.66%	36.66%	73.15%

Table 3. Results of proposed method.

Mean Square Error	The number of repetitions in stopping time	Recall None-Diabetes	Precision None-Diabetes	Recall Diabetes	Precision Diabetes	Accuracy
0.07	700	90.85%	96.57%	81.74%	61.73%	89.48%
0.01	2834	97.2%	94.38%	79.16%	31.66%	69.12%
0.08	608	88%	94.82%	75%	54.54%	85.9%

Table 4. MLP comparison with intelligent system.

Method name	The Mean Square Error	The number of repetitions in stoppage time	Accuracy
Neural network	0.01	3758	63.75%
Pre-processing + Neural network		2834	69.12%
Neural network	0.07	896	80.78%
Pre-processing + Neural network		700	89.48%
Neural network	0.08	695	73.15%
Pre-processing + Neural network		608	85.9%

After multilayer perceptron training, network performance is evaluated based on test dataset. Table 2 provides the obtained results for various values of mean square error. Finding the best mean square error is affective in network performance. The smallest value from the optimum point (mean square error optimum value) results in overtraining of learning process in the network. As seen in table 2, 0.01 of accuracy rate decreases the classification. On the other hand, by increasing the mean square error, the learning process may not be completed fully and consequently, the network will not have a

good performance. By trial and error method, the optimum amount of mean square error can be measured. Here, based on accuracy criterion, 0.07 is a suitable amount to be considered as the stopping condition in learning. The results of the proposed method are shown in Table 3. In this section, first two methods of neural network and proposal method will be evaluated in the same condition and training data. In Table 4, the results achieved from each method are shown.

According to the presented results in the table 4, the result achieved here shows that the mean square error of 0.07 has increased to

8.7% of network accuracy by doing this pre-processing. The more network accuracy rate increases, the more the prediction of diabetes catching increases, so according to the achieved output from this pre-processing, the number of years the patient passed with the high serum ferritin has a crucial role in catching diabetes. On other hand, the mean blood glucose in recent years can be considered as another symptom of diabetes. Finally, 89.48% of diabetes catching can be predicted in patient having thalassemia, performing the proposal method.

6. CONCLUSION

Diabetes mellitus is one of the most serious complications for iron overload (hemochromatosis) due to blood transfusions in patients with β -thalassemia that is detectable by measuring glucose. The aim of this study is to provide a model to predict risk of catching diabetes in patients having β -thalassemia. The effecting factors such as: gender, age, parental family relationship, type of thalassemia, the spleen, gall bladder and liver condition, the age of blood transfusion, blood transfusion intervals, the number of received blood units in each period, the condition of iron overload, the age of start iron chelation therapy, the average of heart T2 rates, the liver T2 and LIC, the number of years having MRI, serum ferritin level, glucose and the number of years the patient was observe are applied. These factors were collected for 255 patients having β -thalassemia major and intermedia from Zafar Adult thalassemia clinic in Tehran.

Based on the obtained results in the previous section, the best accuracy rate in multilayer perceptron with mean square error 0.07 is 80.78%. In this article, in order to improve system performance, pre-processing

was carried out on the features "serum ferritin level", "glucose" and "the number of years the patient was under observe". According to Table 4, the accuracy rate is 89.48% after pre-processing that is increased 8.7% in comparison with prior mode. So, the ability to predict diabetes is more after pre-processing.

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COMPLIANCE WITH ETHICAL STANDARDS

Compliance with Ethical Standards

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

ETHICAL APPROVAL

All procedures performed in this paper were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

INFORMED CONSENT

Informed consent was obtained from the participant included in this study.

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