ORIGINAL ARTICLE

Developing an Intelligent Tool for Breast Cancer Prognosis Using Artificial Neural Network

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Abstract- Today, there is ample scientific evidence that Breast Cancer (BC) is a global health challenge given its prevalence and invasive nature. Therefore, early detection of BC can help minimize the devastating effects of the disease. This study aimed to design a Clinical Decision Support System (CDSS) based on the best Artificial Neural Network (ANN) configuration to identify patients quickly. Using a single-center registry, we retrospectively reviewed the records of 3380 suspected BC cases. The independence test of Chi-Square at P<0.01 was utilized to select the most important criteria. Then the different ANN configuration was implemented in the Matlab R2013 environment and compared using some evaluation criteria. Finally, the best ANN configuration was obtained. After implementing feature selection, 20 variables were determined as the most relevant factors. The experimental results indicate that the best performance was obtained by the 20-25-1 configuration with PPV=90.9%, NPV=99.7%, Sensitivity=98.9%, Specificity=97.9%, Accuracy=98.1%, and AUC=0.958. The proposed software can identify cases of BC from healthy individuals with optimal diagnostic accuracy. Additionally, it might be integrated as a practical and helpful tool in natural clinical settings for easy and effective disease screening.

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Introduction

Breast Cancer (BC), one of the most common malignancies, might considerably influence the communities` health (1,2). BC develops early in the glands and mammary ducts and then metastasizes to surrounding tissues, adjacent lymph nodes, and other organs (3-5). Commonly, it is considered a global health burden due to its prevalence and invasive nature(6,7). According to global statistics, one of the most common cancers diagnosed in 2020 was BC (8). Unluckily, many breast malignancies are diagnosed late in the advanced stages of the disease, in which the disease is more likely to spread to surrounding tissues and other organs (9,10). Therefore, continuous screening and early diagnosis of the disease in the early stages are critical in minimizing its devastating consequences and the resulting mortality (11,12). For this aim, the implementation of systematic, scientific and up-to-date screening policies is essential in diminishing the detrimental consequences of the disease (13,14).

Conventional methods, however, are often costly, complicated, time-consuming, and invasive (15,16). On the other hand, different stages and degrees of the disease severity and some ambiguities and unpredictable situations in the disease behavior and outcome have necessitated utilizing new technologies in the diagnosis and screening of the disease (17,18).

Today, it is believed that new technological and non-invasive methods such as Artificial Intelligence (AI) and intelligent systems can be effective in the rapid, accurate, and timely diagnosis of malignancies (19). Besides, it is

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even more pronounced when the early and rapid diagnosis of cancers in the early stages is considered the essential factor for definitive treatment, prevention of unpleasant complications, and increasing the chances of patients' survival (5,9). The utilities, as mentioned earlier, provide in-depth, adequate, and non-invasive analytical capabilities to support the decisions of physicians and other clinical staff over traditional clinical and statistical methods (11,16). Machine Learning (ML) is a subset of AI with many applications in many industries, including healthcare (20,21). Also, the ML plays a very influential role in managing malignancies such as prognosis, screening, diagnosis, and treatment (22,23). In the last few decades, several ML-based methods have been developed for the effective and timely prognosis and screening of BC. These methods will support decisions by extracting discernible patterns and applied knowledge from the raw data set (24,25).

So far, many researchers have studied the application of ML techniques in predicting and diagnosing BC. For example, Mohammed (2021) proposed an intelligent method for the early prognosis of BC with optimal accuracy and precision (26). Heidari (2018) designed a diagnostic decision support system with reasonable diagnostic accuracy to differentiate BC from other similar conditions (22). In addition, Chaurasia's (2020) research showed that the ML techniques-based expert systems enjoy much higher accuracy and capability in rapidly diagnosing the disease (20). Therefore, the present study aimed to effectively and promptly identify and distinguish patients with BC from healthy ones through intelligent ML techniques. For this purpose, multiple Artificial Neural Network (ANN) configurations were compared on the patient clinical data set using evaluation criteria derived from the confusion matrix. To the best of our knowledge, the present study may help physicians in the accurate and timely diagnosis of the disease and, consequently, minimize the severe complications of the disease and the resulting mortality.

Materials and Methods

This study consisted of four steps as follows:

Data gathering and dataset definition

This study aimed to detect the BC cases in suspected people earlier, so the research community was suspicious people referred to Imam Khomeini and Mostafa Khomeini hospitals, Ilam city, West of Iran for BC screening and diagnosing (positive or negative BC). In our study, data mining models were trained and evaluated on the data of suspected BC cases extracted from the Electronic Medical records (EMR) of the mentioned centers. The Ilam University of Medical Science ethics board approved the study design (Ethics code: IR.MEDILAM.REC.1399.294). The data of 3538 suspected cases were considered in this respect. Among them, 2928 and 610 cases belonged to negative and positive BC, respectively.

Each case in the EMR included 32 defining features categorized into five main classes of BC diagnosis: demographics, epidemiologic, nutritional, personal, and family history of diseases and interventions. All factors affecting the BC diagnosis stored in EMR have been shown below. Also, they were considered independent factors for BC diagnosis in this study. This study's dependent or output variable was the BC diagnosis with two values of 0 and 1, which were associated with the negative and positive BC diagnosis, respectively.

BC diagnostic variables

- **Demographics:** age, nationality, job, educational level, marital status, waist size, and Body Mass Index (BMI).

- **Epidemiological:** alcohol drinking, walking, physical activity, hard job physically, fatness, and optimal physical conditioning.

- **Nutritional:** fruit, vegetable, dairy, salt, fast food, and oil consumption.

- **Personal and family history of diseases:** history of BC, hypertension, hypercholesterolemia, hyperglyceridaemia, hyperlipidemia, diabetes, upper inner quadrant BC, common cold, and BC in the unspecified region, and family history of BC.

- **Personal history of measurements and interventions:** breast investigation, breast sampling, chest radiography.

Dataset preparation

In this study, we used three steps to prepare the data in EMR for building the diagnostic model using different architectures of ANNs. 1- Removing the cases including more than 70% missing values, 2-normalizing the samples with less than 70% % missing, noisy, irrelevant, or outlier values via the appropriate statistical method, and 3- Feature Selection (FS). First, all case records have been reviewed by two Health Information Management (HIM) specialists (R: N and M: SH) with the consultation of one statistician and two cancer specialists analytically. In this step, the cases with more than 70% missing, noisy, irrelevant, or outlier values and didn't have an applicable role for statistical analysis were removed from the study. In the second step, for samples with less than 70% missing, noisy, irrelevant, or outlier values, we applied the mean of nearby points to embed the lost values with the average of surrounding values. In the last, to prepare the dataset for data mining with essential features statistically, we used the FS process to reduce the dataset dimensions. This preprocessing method isolates the noisy, irrelevant, and redundant data from the dataset and boosts the data mining performance. There are many advantages for FS and selecting the best variables in the ML process, such as making easier data understanding and data representation, decreasing proceeding and storage needs, reducing the ML algorithm's time and consequently, increasing the ML algorithm's training speed, improving the ML's performance via deleting the noisy data, selecting the most important predictors, and also barricading from the ML overfitting (27-30). In this study, to acquire the essential factors for diagnosing the BC and reducing the dataset dimension, the independence test of Chi-square (χ^2) was used in this respect. $P<0.01$ was considered for determining the meaningfulness of this relationship statistically.

Artificial neural network modeling

Artificial Neural Networks (ANNs) are computational models which are inspired by natural human brain structure. They also act like humans in the learning process and solve the problems of experiencing past information patterns (31,32). The ANNs mainly have three computational layers in their structure, including the input, hidden, and output layers. The ANN's structural layers consist of several neurons to perform the ANN's computation and introduce the solution. The input layer representing independent variables acquires the data, attributes, or signals from the external perimeter. It normalizes the inputs to precise values using the activation functions to facilitate computational performance. The middle layer is the hidden or intermediate, including many neurons that perform the most computational process in ANNs to extract the data patterns from the normalized input data. The output layer representing dependent variables also consists of the neurons responsible for representing the output results (31,33-35). Four ANN configurations depend on the layer's structures and how the neurons are arranged. These classifiers include simple-layer feed-forward with one hidden layer, which has a more straightforward computational capability. Multiple-layer feed-forward with two or more hidden layers for complicated computations. Feedback using the outputs results from neurons as feedback of the inputs. And mesh architectures which each of them used in different applications (33). In this study, the feed-forward backpropagation ANN type was used because of its suitability for training the ANN and the high frequency.

Another parameter that is important for ANNs is the training process. It's the ANN's behavior in the computational process and detecting the patterns. This process can be defined as mathematical functions that coordinate the weight of synapses to the threshold of the ANN's neurons for solution generalization. In other words, after determining the relationship between the input and target values during the learning process, the ANN can compute the expected output values based on the given input values (34,35). In this study, we used the tansig function as the ANN's transfer function for training the ANN because of its high speed in training the ANN without considering the exact type of ANN's activation function. Also, in this study, the Levenberg Marquardt was applied as the ANN's learning function for its high-speed execution. For this purpose, the number of epochs was set at 1000, and the training time was infinitive considering the high speed of training.

Selecting the artificial neural network configuration

To select the best ANN configuration, we first compared different ANN structures using the various performance criteria such as PPV (Formula 1), NPV (Formula 2), sensitivity (Formula 3), specificity (Formula 4), accuracy (Formula 5), and AUC obtained from the confusion matrix (Table 1).

Table 1. Confusion matrix

		Predicted cases	
		+	-
Real cases	+	True Positive	False Positive
	–	False Negative	True Negative

Equation 1: $\mathrm{PPV} = \frac{\mathrm{TP}}{\mathrm{TP+FP}}$

Equation 2: $\mathrm{NPV} = \frac{\mathrm{TN}}{\mathrm{TN+FN}}$

Equation 3: $\mathrm{Specificity} = \frac{\mathrm{TN}}{\mathrm{TN+FP}}$

Equation 4: $\mathrm{Sensitivity} = \frac{\mathrm{TP}}{\mathrm{TP+FN}}$

Equation 5: $\mathrm{Accuracy} = \frac{\mathrm{TP+TN}}{\mathrm{TP+FN+FP+TN!}}$

In Table 2, the True Positive (TP) and True Negative (TN) cases were associated with the number of positive and negative BC cases classified correctly. False Positive (FP) and False Negative (FN) were related to the number of positive and negative BC cases classified falsely. In this study, we added one neuron to the hidden layer, then calculated and compared the different configurations of the ANN using the mentioned performance criteria and obtained the best structure of the ANN. 70% of positive and negative BC cases were used for training the ANN. Also, 10% and 20% were used to validate and test the ANN, respectively. In this study, to investigate the capability of the selected ANN's configuration in training, validating, and testing process, the Mean Squared Error (MSE) and Error histogram diagram were applied in this regard. Finally, the CDSS user interface of the ANN for diagnosing the BC was designed in the MATLAB R2013 environment.

Table 2. The Chi-square (χ2) amount of the selected BC diagnosis factors at *P*<0.01

no	Variable	Type	Value codes in the dataset	Frequency or Mean ± SD	χ^2	*P*
1	Personal history of BC	Binominal	Unknown (9) Haven’t (0) Have (1)	Unknown (179) Haven’t (959) Have (2242)	18.885	0.001
2	History of breast sampling	Binominal	Unknown (9) Haven't (0) Have (1)	Unknown (223) Haven't (1159) Have (1998)	15.443	0.007
3	History of chest radiography	Binominal	Unknown (9) Haven't (0) Have (1)	Unknown (93) Haven't (1017) Have (2270)	16.665	0.001
4	Family history of BC	Binominal	Unknown (9) Haven't (0) Have (1)	Unknown (408) Haven't (2403) Have (569)	20.221	0.001
5	Hypertension	Binominal	Haven’t (0) Have (1)	Haven’t (2650) Have (730)	13.263	0.006
6	Alcohol consumption	Binominal	Haven’t (0) Have (1)	Haven’t (2956) Have (424)	11.985	0.005
7	hypercholesterolemia	Binominal	Haven’t (0) Have (1)	Haven’t (3189) Have (191)	9.225	0.005
8	hyperglyceridaemia	Binominal	Haven’t (0) Have (1)	Haven’t (3356) Have (24)	5.454	0.009
9	hyperlipidemia	Binominal	Haven’t (0) Have (1)	Haven’t (3169) Have (211)	4.773	0.008
10	Diabetes	Binominal	Haven’t (0) Have (1)	Haven’t (3284) Have (96)	10.256	0.005
11	Fatness	Binominal	Haven’t (0) Have (1)	Haven’t (3283) Have (97)	11.674	0.005
12	Upper quadrant breast mass	Binominal	Haven't (0) Have (1)	Haven't (3367) Have (13)	15.774	0.004
13	Unspecified region of breast mass	Binominal	Haven't (0) Have (1)	Haven't (3280) Have (100)	12.442	0.005
14	Exercise (hours in day)	Polynomial	Low (0) Medium (1) High (2)	<0.5 (1079) 0.5-1 (2015) > 1 (286)	13.334	0.008
15	BMI	Numerical	-----------	24.152 ± 11.453	14.667	0.003
16	Age	Numerical	-----------	46.376 ± 11.868	13.656	0.005
17	Fruit consumption (Grams per day)	Polynomial	Low (0) Medium (1) High (2)	<100 (911) 100-200 (2134) >200 (335)	8.326	0.004
18	Vegetable consumption (Grams per day)	Polynomial	Low (0) Medium (1) High (2)	<150 (791) 150-300 (2132) >300 (457)	7.421	0.002
19	History of breast investigation	Binominal	Haven't (0) Have (1)	Haven't (1042) Have (2338)	5.425	0.007
20	The hard job with physical activity	Binominal	Haven't (0) Have (1)	Haven't (2945) Have (435)	6.727	0.009

Results

After removing the samples with more than 70% missing, noisy, or outlier values, 128 and 30 records belonging to the negative and positive BC cases were excluded from the study. Therefore, out of 3538 primary suspected cases, 2800 negative and 580 positive samples have remained in this study. The whole of positive and negative BC cases were women (100%) with an average age of 33.227 ± 11.113 and 41.224 ± 8.882, respectively. The result of using the independence test of Chi-square (χ^2) at P<0.01 is shown in Table 2.

Based on the information given in Table 2, 20 variables gained a meaningful relationship with the BC as the dependent variable statistically at P<0.01. Also, the three variables of the personal history of BC (χ^2=18.885, P=0.001), history of chest radiography (χ^2=16.665, P=0.001), and family history of BC (χ^2=20.221, P=0.001) with the highest Chi-square at P<0.01 were considered as the essential diagnostic factors for BC than other variables in this study. The results of comparing some different ANN configuration is demonstrated in Table 3.

Table 3. Different ANN's configuration with performance criteria

No	ANN architecture	Best training epochs	PPV	NPV	Sensitivity	Specificity	Accuracy	AUC
1	20-1-1	10	60.9%	95.7%	80.7%	89.2%	87.8%	0.795
2	20-2-1	23	61.5%	95.2%	78.3%	89.8%	87.8%	0.798
3	20-3-1	15	64.8%	96%	81.7%	90.8%	89.2%	0.843
4	20-4-1	23	65.4%	96.2%	82.9%	91.2%	90.2%	0.851
5	20-5-1	16	73.4%	97%	85.1%	94.8%	92.1%	0.846
6	20-6-1	20	77.7%	97.1%	86.4%	94.8%	93.4%	0.875
7	20-7-1	24	79.6%	95.3%	87.7%	95.3%	94%	0.865
8	20-8-1	16	78.5%	97.4%	88.2%	94.6%	93.5%	0.871
9	20-9-1	17	82.2%	97.7%	89.5%	96%	96.9%	0.911
10	20-10-1	15	83.2%	97.4%	88.8%	96.2%	95%	0.906
11	20-25-1	36	90.9%	99.7%	98.9%	97.9%	98.1%	0.958

Based on the information provided in Table 3, we observed that adding one neuron in ANN's hidden layer increased the performance rate of different configurations. Especially in classifying the positive cases (sensible difference in PPV and sensitivity) as far as, in the ANN with the structure of 20-25-1 at 36 training epochs with 20 neurons in the input layer (input variables), 25 calculation neurons in the hidden layer, and one neuron in the output layer (BC diagnosis), the model performance has reached the best (PPV=90.9%, NPV=99.7%, Sensitivity=98.9%, Specificity=97.9%, Accuracy=98.1%, and AUC=0.958). The training, validation, and test modes of the confusion matrix of the ANN are shown in Figure 1.

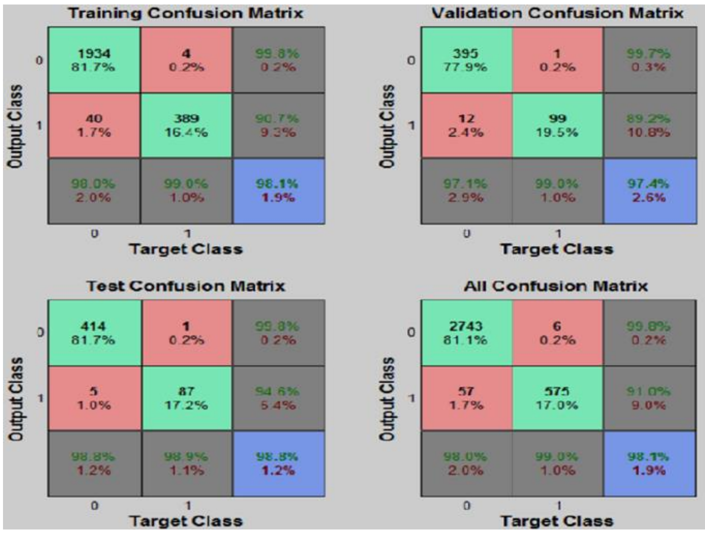

Figure 1. All different ANN modes confusion matrix

Based on Figure 1, the ANN in the test mode gained a higher performance capability than others, with TP=17.2%, FN=0.2%, FP=1%, and TN=81.7%. The validation modes was slightly lower than other with TP=19.5%, FN=0.2%, FP=1.7%, and TN=77.9%. Generally, the ANN with the selected configuration in all modes obtained high performance. The ANN learning error reduction during the training process based on the

MSE diagram of the ANN has been shown based on Figure 2.

Based on Figure 2, by considering the validation error rate as the criteria for the ANN's error-correction learning, we observed that at the 30th epoch of the selected ANN, the validation error rate with MSE=0.22 reached the minimum amount. Therefore, the ANN at this step had the most pleasant performance in this respect. Also, the training and test modes of the ANN acquired a minimal error rate with 10^{-2}<MSE<10^{-1}. In Figure 3, the BC diagnosis's clinical decision support system (CDSS) user interface was designed in MATLAB R2013 environment in modular codes.

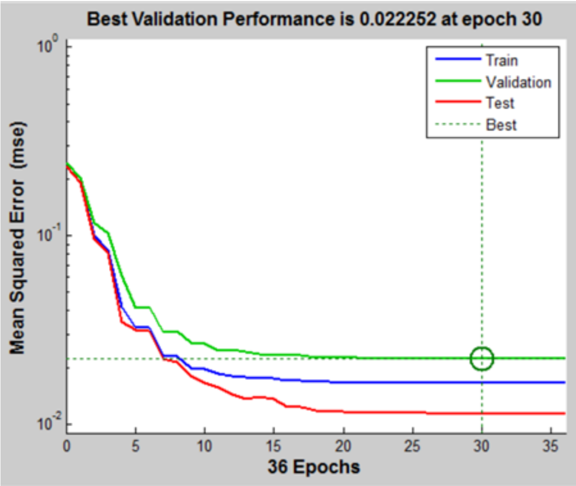

Figure 2. The MSE of the ANNs

Figure 3. The developed CDSS user interface for BC diagnosis

Discussion

Owing to the sensitive, ambiguous, and multidimensional nature of BC (36) and the ever-increasing number of cases coupled with relatively complex para-clinical evaluations, the CDSS technologies equipped with ML algorithms play an essential role in rapid patient identification, enhance diagnostic services quality and provide customized and patient-centered care (37,38). Thus, the primary purpose of this study was to evaluate some ANN configurations in diagnosing BC and differentiating between patients from healthy individuals to improve the treatment quality and the effectiveness of clinical decisions. Unlike many performed studies, which often used ANN models to diagnose the disease on visual data (mammography images), the present study applied clinical data and various ANN configurations to identify healthy individuals from those suffering from BC. Reportedly, the ANN techniques might fast and effectively track and identify trends and patterns affecting the emergence and development of breast malignancies (39,40). Numerous studies have been conducted in this field to analyze, classify, and differentiate BC cases from healthy ones. For example, Irmak *et al*., (2021) designed an optimal diagnostic expert system by evaluating the various structures of the ANN model to differentiate BC cases from healthy individuals with an accuracy of 99.36% (41). Besides, Naveed (2021) proposed a CDSS based on various data mining methods to classify the risks related to BC. Ultimately, the Feed Forward Neural Network (FFNN) model, with an accuracy of 99.03%, represented the highest case classification (42). In addition, Alka (2021) reported the superiority of the multilayer neural network structure in the diagnosis of BC and its effective screening (accuracy=97.7%) (17). In another study by Rawal *et al.*, (2021), they implemented two data mining models to diagnose BC, and ultimately the ANN model presented a better capability for disease screening (40).

Furthermore, Turjman (2021) suggested that the ANN model, with an accuracy of 99.11%, recorded the highest score in the diagnosis of BC and the differentiation of healthy cases from the affected ones (43). Similarly, Ali (2019) reported that the network model would be more capable of effectively predicting and screening BC (44). Mehdy (2017) concluded that the ANN model, with 92% accuracy, achieved the best performance in identifying and differentiating BC from healthy cases (4). Also, the selected data mining models comparison in Hazra's (2020) study showed that the ANN model with 98.55% accuracy was better able to predict and diagnose BC (44). Plus, Leszczyński *et al*., (2019) designed an optimal ANN-based model for predicting and prognosis BC. Finally, the proposed model gained high potential in diagnostic screening (39). In a similar study, Singhal (2019) revealed that diagnosing BC malignancies through diagnostic decision support systems based on the ANN model is more accurate than other models (45). Sepandi *et al*., (2018) concluded that the ANN model with an accuracy of 90% is the best model for diagnosing BC (46).

Hence, the present study aimed to identify and effectively screen BC by comparing different network model configurations with earlier studies. Therefore, initially, essential and effective variables were identified using the chi-square test at $P<0.01$. The results represented that 20 variables were selected as the input of the network model out of a total of 32 variables. Then eleven configurations were implemented for the network model. The results showed that the 20-25-1 structure reported higher performance based on the evaluation criteria. Finally, the user interface of CDSS software in the MATLAB environment was designed and integrated for clinical applications to create an interactive environment with the physician. Therefore, the design of the final software user interface is one of the strengths of the present study, which was not addressed in the studies mentioned earlier.

Notwithstanding the high capability of the proposed model in rapid and effective disease prediction and screening, along with a user-friendly and straightforward interface for integration with natural clinical environments, the generalizability of the proposed model is subject to certain limitations. For instance, retrospective and single-center research design, the small number of samples in the selected database, and the evaluation of merely one algorithm (ANN) were considered our study limitations. In addition, the retrospective nature of the data collection process made data records incoherent, incomplete, and full of errors and abnormalities. In the future, the performance accuracy of our model and its generalizability will be enhanced if we test more ML techniques in the more prominent, multicenter, and prospective dataset, which is equipped with more qualitative and validated data.

The ANN-based intelligent models can help physicians diagnose breast malignancies early and provide timely and customized treatment plans. In the present study, different ANN configurations were implemented to develop an effective diagnostic model for BC. Thus, comparing the performance of different designs implemented in the network model based on various evaluation criteria showed that the 20-25-1 structure could be applied as a suitable diagnostic model with high performance in timely and accurate diagnosis of the disease. Therefore, the CDSS software user interface was ultimately designed based on this structure and implemented in the MATLAB R2013 environment.

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