Applications of Logistic Regression and Artificial Neural Network for ICSI Prediction

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Abstract: *The third most serious disease estimated by Word Wide Organization after cancer and cardiovascular disease is the infertility. The advanced treatment techniques is the Intra-Cytoplasmic Sperm Injection (ICSI) procedure, it represents the best chance to have a baby for couples having an infertility problem. ICSI treatment is expensive, and there are many factors affecting the success of the treatment, including male and female factors. The paper aims to classify and predict the ICSI treatment results using logistic regression and artificial neural network. For this purpose, data are extracted from real patients and contain parameters such as age, endometrial receptivity, endometrial and myometrial vascularity index, number of embryo transfer, day of transfer, and quality of embryo transferred. Overall, the logistic regression predicts the output of the ICSI outcome with an accuracy of 75%. In other parts, the neural network managed to achieve an accuracy of 79.5% with all parameters and 75% with only the significant parameters.*

Keywords: *Artificial Neural Network (ANN), Assisted Reproductive Treatment (ART), In-Vitro Fertilization (IVF), ICSI, logistic regression.*

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1. Introduction

Intra Cytoplasmic Sperm Injection (ICSI) is an option for couples who naturally fail to achieve pregnancy. Yet, this option is stressful and expensive. Thus, couples may refrain from treatment if the initial evaluation indicates a low probability of success [4].

The choice of the best stimulation protocol, culture technique, embryo selection may improve ICSI outcome, but also embryo transfer technique is one of the most important determinants of this outcome [1].

Despite numerous developments in assisted reproduction techniques, Clinical Pregnancy Rate (CPR) in In-Vitro Fertilization (IVF) and ICSI remain relatively low. It has been estimated that up to 85% of the non-genetically screened embryos replaced into the uterine cavity fail to implant. The cause of this low CPR may reside in the technique of embryo transfer, the endometrial receptivity, or the capacity of the embryo to properly invade the endometrium [5].

Nowadays, the high resolution and frequency of Transvaginal Ultrasound (TVUS) is used to improve the assessment of endometrial receptivity during Assisted Reproductive Treatment (ART) cycles.

Ultrasound parameters including endometrial thickness, endometrial pattern, endometrial volume and Doppler study of uterine arteries and endometrial blood flow have been used to assess endometrial receptivity during IVF procedure [1, 5, 17] but till now no published studies on myometrial vascularity, endometrial and myometrial mean grey and the thickness at the site of embryo.

Some data suggest that the results of human IVF may be affected by the site of the uterine cavity where embryos are released. Some studies demonstrates that site of embryo transfer has significant difference on reproductive outcome [12, 13].

The probability of success rate by embryo transfer cannot be predicted accurately. So many studies continue to test new methods to implement a statistical model including different parameters affecting clinical pregnancy rate. The actual state needs to build new systems to assist Human Mind. Many of the recent studies tackle the relations between some variables and the outcomes of IVF for example $\chi 2$ test, student t-test [2, 17], logistic regression [13] and other tests.

Traditional methods of statistical analysis are to determine a precise reason behind infertility and to provide effective predictors of treatment. The relationship between the analyzed factor and treatment outcome can be determined by univariate analysis. However, multivariate analysis (multivariate logistic regression) allows to predict the pregnancy by providing a high accuracy model [7].

Data mining is a term used by many methods of studies to analyze and classify the medical data. SIRISTATIDIS advocate to use the Artificial Intelligence techniques in analyzing information concerning reproductive medicine [14]. Different studies applied several techniques in prediction of ICSI outcome such as: Support Vector Machine (SVM) and Random Forest [16], Naïve Bayes classifier [8], Discriminant Analysis [9] and Ranking algorithm (SERA) [14].

There are high hopes for the Artificial Neural Network technique, for which effectiveness of pregnancy predictive has already been confirmed and it can replace the tradition statistical prediction methods such as regression analysis [7]. This classifier is conceived to learn information, to generalize and to model any kind of linearity or nonlinearity with multidimensional high accuracy [6].

Different studies used Artificial Neural Network (ANN) to predict results of ICSI treatment, but these studies differed by the choice of their parameters which are the input of the model. Kaufmann used the age, number of eggs recovered, number of embryos transferred and whether there was embryo freezing and the network achieved an accuracy of 59% [6]. Another study used data that include duration of infertility, body mass index, endometriosis, tubal causes, sperm concentration, number of oocytes retrieved, number of embryos transferred and ICSI treatment and this work shows 73% of accuracy in their result [3]. Also, a study by Milewski [10] used the patient's age, number of cells and embryos at various developmental stages, and sperm characteristics were taken into account as numerical independent variables.

The aim of our paper is to study the significant parameters and predict the success rate of ICSI by using the logistic regression then construct a supervised learning ANN to predict a new result. Finally, a comparison between the results of three models:

1. The accuracy of prediction of logistic regression.
2. The accuracy of prediction of ANN using 19 parameters as inputs.
3. The accuracy of prediction of ANN using as inputs 8 parameters which are the significant ones.

2. Parameters of the Study

2.1. Definition of ICSI

ICSI is a process of fertilization where an ovum is joined with a sperm outside the body, in a specialized laboratory. The fertilized ovum (embryo) is allowed to grow in a protected environment for some days (culture cycle for 2–6 days) before being transferred into the woman's uterus. This procedure increases the chance that a pregnancy will occur. The process includes observation and stimulating a woman's ovulatory process, taking an ovum or ova from the woman's ovaries and giving sperm the chance to fertilize them in a culture media. The fertilized ovum (zygote) undergoes embryo culture for 2-6 days, and then moved to the same or another woman's uterus, with the hope of establishing a successful pregnancy.

2.2. Definition of all Parameters

The parameters that have been used in our study are suggested by the gynecologist Dr. Chadi Fakih and related to some study done in his center and defined as follows:

- X_1=Age : age of the patient
- X_2=Tentative: number of previous ICSI trials.
- X_3=Embryo Transfer (ET): number of transferred embryos per ICSI cycle.
- X_4=Transfer day: day of transfer.
- X_5=Endometrial Thickness (ET): defined as the maximal distance between the echogenic interfaces of the myometrium and the endometrium, measured in the plane through the central longitudinal axis of the uterus.
- X_6=site of embryo: distance between the spot of embryo transfer and the fundus of uterus.
- X_7=Endometrial Volume (EV).
- X_8=Endometrial Mean Grey (Endo MG): grey-level histogram of the uterine- endometrium.
- X_9=Endometrial VI (Endo VI): vascularization index which represents the vessel density in the endometrium.
- X_{10}=Endometrial FI (Endo FI): flow index which represents the intensity of blood flow in the endometrium.
- X_{11}=Endometrial VFI (Endo VFI): vascularization flow index which represents the endometrial perfusion.
- X_{12}=Myometrial volume (Myo V).
- X_{13}=Myometrial Mean Grey (Myo MG): grey-level histogram of the uterine- myometrium.
- X_{14}=Myometrial VI (Myo VI): vascularization index which represents the vessel density in the myometrium.
- X_{15}=Myometrial FI (Myo FI): flow index which represents the intensity of blood flow in the myometrium.
- X_{16}=Myometrial VFI (Myo VFI): vascularization flow index which represents the myometrial perfusion.
- X_{17}=Thickness at the site of embryo: thickness of endometrium at the site of embryo.
- X_{18}=Endometrial pattern (Echogenicity): defined as the relative echogenicity of the endometrium and the adjacent myometrium. We have two types of echogenicity: triple line and homogeneous.
- X_{19}=Embryo grading: quality of transferred embryo determined by the embryologist based on morphology.

3. Experimental Protocol

3.1. Data Collection

Data was collected from all patients (132 patients) undergoing ICSI procedure at ALHADI IVF Center between January and April 2018. It is important to note that all 132 patients have accepted to participate to this study.

For each patient, the dataset includes independent features like demographic, clinical parameters, endometrial and myometrium 3D power Doppler flow indices. The result of dataset analysis has one dependent variable, the value 1 (success) if the woman had a clinical pregnancy (defined as the detection of fetal heart beat on the ultrasound examination) and the value 0 (failure) if the patient had no pregnancy.

The dataset includes 19 independent elements; 16 of them are referred to the female, and 3 are referred to the embryo and transfer data.

3.2. Measurement of all Parameters

Basically, the high resolution of ultrasound machine (WS80A) from Samsung, Medison enables us to examine clearly the different implantation aspects: endometrial thickness, endometrial morphological patterns, endometrial/myometrial volume, endometrial/myometrial mean grey, thickness at the site of embryo and finally the site of embryo.

Pulsed and color Doppler is used to indicate different variables of uterine and endometrial/myometrial perfusion which is VI, FI, VFI that are also used as receptivity factors.

We can measure all the parameters by using the three sections: coronal, sagittal and transverse of 3D sonography, the values of the two features, age and tentative where taken directly from each patient, the number of embryo transfer and the transfer day; where given by the embryologist.

4. Statistical Study: Logistic Regression

Logistic regression analyses the relationship between multiple independent variables and a categorical dependent variable, and determines the probability of occurrence of an event by fitting data to a logistic curve. Many parts are involved to evaluate the logistic regression model. In our work, the logistic regression is used to assess the model, select the significant parameters and finally, evaluate the predictive accuracy or discriminating ability of the model.

We adopt the logistic regression to indicate the significant independent variables related to our dependent variable and to predict the probability of being pregnant.

The Wald test (also called Wald Chi-Squared Test) is a significant way to find the explanatory variables in a model.

In the univariate case, the statistic is:

$$\frac{(\hat{\beta}-\beta_0)\char`^2}{var(\hat{\beta})} \tag{1}$$

This is compared against a Chi-Squared distribution with one degree of freedom, where β̂ is the estimated value of β.

$$\begin{gathered} H_0: \beta_j = 0 \\ H_1: \beta_j \neq 0 \\ wald = \frac{\beta_j\char`^2}{\hat{\sigma}\char`^2(\beta_j)} \sim \chi2 \end{gathered} \tag{2}$$

If p-value> α then we reject H_0 and so the variable is significant [6].

4.1. Result of Wald Test

According to the Table1, the significant variables are: Age, Transfer day, Site of Embryo, Endometrial Mean Grey (Endo MG), Endo VFI, MYO VI, MYO VFI, Embryo grading.

4.2. Classification Table of the Logistic Regression

The classification table (Table 2) is a method to evaluate the predictive accuracy of the logistic regression model. In this table the observed values for the dependent outcome and the predicted values (at a user defined cut-off value) are cross-classified. The cutoff value is 0.5 (by default); all predicted values above 0.5 can be classified as predicting an event, and all below 0.5 as not predicting the event. In an analogy with medical diagnostic testing, we can consider the test sensitivity which is the ability of a test to correctly identify those who are pregnant $sensitivity = \frac{a}{a+b}$. Andthe test specificity is the ability of the test to correctly identify those who are not pregnant $specificity = \frac{d}{c+d}$. Higher sensitivity and specificity indicate a better fit of the model [11].

Table 1. Results of the variables in the equation.

Variables	B	Sig.
X_1	-0.105	0.000
X_4	0.750	0.002
X_6	-0.932	0.025
X_8	-0.035	0.022
X_{11}	-0.478	0.042
X_{14}	0.114	0.021
X_{16}	-0.265	0.035
X_{19}	4.251	0.000

Table 2. Table represents a sample of classification table (a, b, c and d are number of observations in the corresponding cells).

	Predicted	
Observed	1	**0**
1	a	b
0	c	d

4.3. Results of the Model

The logistic model for the probability of success is:

$$\hat{\pi}(X_1, X_4, X_6, X_8, X_{11}, X_{14}, X_{16}, X_{19}) =$$

$$P(Y = 1/X_1, X_4, X_6, X_8, X_{11}, X_{14}, X_{16}, X_{19}) =$$

$$e^{\wedge}(-0.105x\_1 + 0.75x\_4 - 0.932x\_6 - 0.035x\_8 - 0.478x\_11 + 0.114x\_14 - 0.265x\_16 + 4.251x\_19)/(1 + e^{\wedge}(-0.105x\_1 + 0.75x\_4 - 0.932x\_6 - 0.035x\_8 - 0.478x\_11 + 0.114x\_14 - 0.265x\_16 + 4.251x\_19)) \quad (3)$$

To obtain the classification table using the logistic regression the cutoff value by default is set to 0.5. Later we can find the exact cutoff value by using the ROC curve.

If π^ ≥0.5 => pregnant (4)

Otherwise => not pregnant

The classification table (Table 3) shows that this model allows us to correctly classify: 64/76=84.2 % of the subjects where the predicted event (pregnant) was observed. This is known as the sensitivity of prediction that is the percentage of occurrences correctly predicted. We also see that this rule allows us to correctly classify 35/56=62.5 % of the subjects where the predicted event was not observed, this is known as the specificity of the prediction that is as the percentage of non-occurrences correctly predicted. Overall all our prediction was correct 99/ (132) =75.0 %.

The Receiver Operating Characteristics (ROC) represents the sensitivity with respects to the 1-Specificity. This graph illustrates the ability of classifier to distinguish between two classes. If the points are in the upper- left corner we have a perfect test. In "Figure 1", the shape of the ROC curve of the logistic regression showed an area of 0.83. This indicates that our classification model is good.

5. Artificial Neural Network

Artificial Neural Networks are systems inspired by the biological neurons of the brain which is learned by experience. An ANN is based on a collection of connected nodes called artificial neurons which loosely model the neurons in a biological brain. The artificial neural network is structured with many different layers that made up by number of neurons.

Table 3. Classification table for the model.

Observed	**Predicted**		
	Response		**Percentage correct**
	no pregnant	**pregnant**	
Response no pregnant	35	21	62.5
pregnant	12	64	84.2
Overall Percentage			75.0

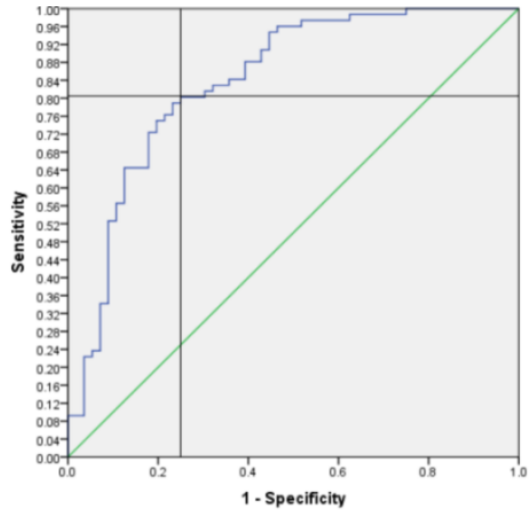

Figure 1. Represents the ROC curve for the logistic regression.

Each neuron receives several numerical inputs; each of them is multiplied by a weighting factor. These products are summed and fed through the transfer function to generate the output of the network [6].

In our study area, ANN model is a feed-forward ANN in a supervised learning algorithm. Our structure model has a single hidden layer with 10 nodes, input (8 or 19) and one output. In a layer network, there are no connections between any two neurons and two subsequent layers are totally connected. The hidden layer uses the non- linear continuous neuron that has a sigmoid function.

The structure of ANN is composed from three layers:

a. *Input layer*: 8 nodes used the significant parameters as inputs and another network used 19 nodes to take all parameters not just the significant one as inputs.
b. *Hidden layer*: the number of nodes used in the hidden layer may be varied as per the validation data. (Experimentally, the hidden layer is one with 10 nodes).
c. *Output layer*: output layer of the constructing neural network is for producing success rate of ICSI treatment (one output node).

A study on the data division for developing a neural network model indicates that the division of data into three sets: training, testing and validation can have a significant effect on the performance of the model. SHAHIN shows that the proportion of the data used for the network influences the model performance but there is no relationship between the proportion data used in each subset and the model performance [15]. So, in our work the best results are obtained with a random division for the three subsets with partition: training set (50%), a validation set (15%) and a test set (35%).

In order to train a neural network to perform some task, we must adjust the weights of each unit in such a way that the error between the desired output and the actual output is reduced. This process requires that the neural network compute the error derivative of the weights. In other words, it must calculate how the error changes as each weight is increased or decreased slightly.

The back propagation algorithm is the most widely used method for determining the derivative of the weights. The back-propagation algorithm is easiest to understand if all the units in the network are linear. The training stops when this reaches a sufficiently low value. We used the validation set for parameter selection and to avoid over fitting. Finally, the accuracy of the model on the test data gives a realistic estimate of the performance of the model on completely unseen data and in order to confirm the actual predictive power of the network.

5.1. Application with all Parameters

The second vertical column has 9 instances of pregnant that was misclassified as no pregnant by the classifier (false negative). In addition, there are 18 non pregnant instances that were classified as pregnant (false positive).

The accuracy percentage with all parameters is 79.5%.

In Figure 2 the shape of the all ROC increased in the corner to 0.86 this indicates a good classification.

Table 4. Represents the all confusion matrix with all parameters as inputs.

		Traget Class		
		0	1	
Output Class	0	38 28.8%	9 6.8%	80.9% 19.1%
	1	18 13.6%	67 50.8%	78.8% 21.2%
		67.9% 32.1%	88.2% 11.8%	79.5% 20.5%

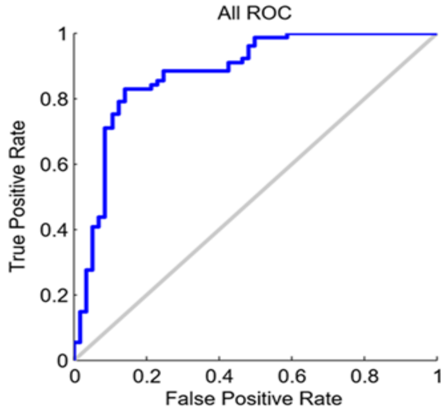

Figure 2. Receiver Operating Characteristics (ROC) for the network with all parameters as inputs.

Figure 3. Represent the neural network training performance.

The performance of the network using all the parameters as inputs indicates the iteration at which the validation performance reached a minimum value of error. The best performance is 0.65015 which is taken from the epoch 12 having the lowest validation error as shown in Figure 3.

5.2. Application with Significant Parameters

The second vertical column has 9 instances of pregnant that was misclassified as no pregnant by the classifier (false negative). In addition, there are 24 non pregnant instances that were classified as pregnant (false positive).

The accuracy percentage with the significant parameters is 75.0%.

Table 5. Represents the all confusion matrix for the network with significant parameters as inputs.

		Target Class		
		0	1	
Output Class	0	32 24.2%	9 6.8%	78.0% 22.0%
	1	24 18.2%	67 50.8%	73.6% 21.2%
		57.1% 42.9%	88.2% 11.8%	75.0% 25.0%

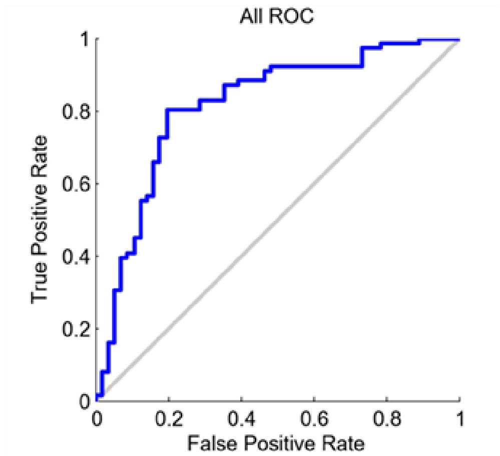

Figure 4. Represents the ROC curve for the neural network with significant parameters as inputs.

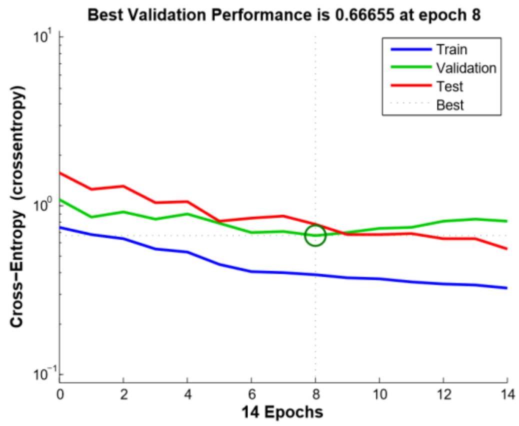

Figure 5. Represent the neural network training performance.

In Figure 4 the shape of the all ROC increased in the corner to 0.83 which indicated good classification in our work, but it is worse than in the previous work.

The performance of the network using all the parameters as inputs indicates the iteration at which the validation performance reached a minimum value of error. The best performance is 0.66655 which is taken from the epoch 8 having the lowest validation error as shown in Figure 5.

6. Discussion and Conclusions

ICSI procedure is long, costly and stressful for couples who want to have a baby. Many different factors affect the results of infertility treatment using the ICSI method. Different studies show the correlation between the ICSI outcome and several parameters such as the endometrial receptivity, endometrial vascularity, the quality of embryo, number of embryo transfer, and the site of embryo [2, 5, 13].

The gynocologist in "ALHADI IVF CENTER" sugggest that we have new parameters that affect the outcome of ICSI treatment which are the myometrial vascularity, endometrial and myometrial mean grey, and the thickness at the site of embryo.

Several applications indicate that the combination of statistical methods provides more accurate results than those obtained by the application of single classical technique [11].

In this paper, after introducing the parameters related to the outcome of ICSI procedure. We applied a logistic regression analysis in order to predict the probability of success with the significant variables and to find the classification table. Then we used the neural network techniques with all the parameters and with the significant parameters to classify the outcome of ICSI. This was the first study to describe a correlation between myometrial vascularity and the outcome of ICSI treatment.

Finally, a comparison of the predictive power between the two models shows that in neural network with all used parameters as inputs is more accurate than that of the logistic regression (79.5%). If we compare the results between logistic regression and neural network that used the significant parameters, selected by logistic regression, we deduce that we have the same accuracy of prediction (75%) as illustrated in Table 4. In conclusion, the proposed technique is useful for finding the minimum set of influential parameters in order to predict the success rate of ICSI.

Table 6. Table represents the comparison between the logistic regression and the Neural Network accuracy.

Type of classifier	Accuracy
Logistic regression	75.0%
Neural Network used all parameters as inputs	79.5%
Neural Network used the significant parameters as inputs	75.0%

In a future work, we can continue the study on a bigger data in order to validate the performance of the model. After that we have to perform a new study based on the automatic detection of endometrium, then measuring new parameters, and reclassifying the pregnant response.

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