ICSI Protocol Advisor: A decision support system for infertility protocol suggestion

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Abstract

Intra-Cytoplasmic Sperm Injection (ICSI) is one of the most common infertility treatments in which ovarian stimulation is carried out to extract the eggs from the ovaries. There are three, short, long, and pure treatment protocols of ovarian stimulation that vary by the type of medicine, the dosage of medicine, and the treatment term.

Today, physicians choose an appropriate treatment protocol based on the patient's condition, such as age, and hormonal condition. This could be a relatively subjective and inaccurate method, particularly if the physician is not highly experienced.

The present study investigates whether a decision support system can propose a more objective treatment protocol based on the patients' data and data mining methods like logistic regression, decision tree, and SVM. Such a system draws upon classification methods to propose proper treatment protocols for ICSI. Moreover, a separate module was developed to calculate the success rate of the proposed protocols. The system was tested with real data of treated patients at a Hospital in Tehran, Iran. The results showed the proposed system can predict the most proper treatment protocol with an accuracy of 81.90%.

The proposed system can help inexperienced physicians to feel more confident about their advice.

Keywords: Intracytoplasmic Sperm Injection (ICSI), Protocols in ICSI program, Decision support system, classification techniques, data mining.

1. Introduction

According to the World Health Organization (WHO), Infertility is "a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse" [1]. According to Mascarenhas et al. [2], 1.9% of the women between20 to 44 intend to have a child suffer primary infertility. In other words, 1.9% of these women are unable to have even one child. Moreover, 10.5% of the women experience infertility following the birth of one child, known as secondary infertility. When a couple fails to bear a child, both the man and the woman must be studied for the cause, because the cause can lie in the man, woman, both, or none of them [3- 6].

Infertility may cause social, psychological, and economic consequences [7- 10]. Social isolation, detachment from family and friends, social exclusion, and reduced social interactions could be some of the social repercussions [11]. The psychological fallout from infertility can include a sense of worthlessness, depression, anger, and anxiety [7]. Moreover, infertility treatment is costly and demanding [12- 15].

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Nowadays, various kinds of treatments are conducted to address infertility. Among them, *In Vitro Fertilization (IVF)* and *Intra-Cytoplasmic Sperm Injection (ICSI)* are the most effective [2]. ICSI is a special form of IVF in which ovarian stimulation is carried out to extract the eggs from the ovaries. Then, a sperm is injected into the egg cell, and if the fertilization occurs successfully and the egg is divided, embryos are transferred to the uterus at the 2-8 cell stage. To perform the ovarian stimulation, the short, long, and pure treatment protocols that vary by type of medicine, the dosage of medicine, and the treatment term can be applied [16]. However, the physician takes some patient circumstances like age, and hormonal condition into consideration to choose the optimal treatment protocol.

According to Kononenko [14], the medical diagnosis knowledge can be obtained automatically based on the histories of the previous patients. Furthermore, the recent digital evolutions have led to the development of relatively low-cost and accessible tools for the collection and storage of data in hospitals and medical centers. Hence, considerable data about patients, including their infertility status, is available in the databases of hospitals and various medical centers [14]. The availability of these data has led to the development of medical decision support systems. A medical decision support system is a computer-based system that analyzes the data collected from various sources of information to assist the users in a medical decision-making process [17]. These systems offer various services such as electrocardiogram- detection- delineation, visualization, prediction, diagnosis, and even the proposal of the most suitable treatment protocols in the areas of cancer, infertility, cardiovascular diseases, pulmonary diseases, etc. [18-28]. For example, Lashkari and Firouzmand [29], developed a toolbox to assist physicians in early clinical detection of breast cancer. Initially, Lashkari and Forouzmand [29] improved the quality of the image. Then, some features including statistical, morphological, frequency domain, histogram, and GLCM features were extracted and feature selection was applied [29]. To classify and labeling, some supervised learning algorithms such as Ada boost, SVM, KNN, NB, and PNN were used [29]. Damirchi-Darasi et al. [30] presented an expert system for diagnosing spinal cord disorders. They used type- 2 fuzzy logic system to handle the high uncertainty of diagnosing the type of disorder and its severity [30]. Damirchi-Darasi et al. [30] showed that the accuracy of their proposed system is acceptable. Karimizadeh, Vali, and Modaresi [31] suggested a method to decide about Pseudomonas Aeruginosia infection status in cystic fibrosis patients based on their respiratory sound. The features which were generated from tunable Q-factor wavelet transform were fed into support vector machine and ensemble classifier [31]. Karimizadeh, Vali, and Modaresi [31] achieved an accuracy of 90.3% in identifying Pseudomonas aeruginosa infection in cystic fibrosis patients. Moradi, Modarres, and Sepehri [32] established an innovative data mining framework for analyzing physicians' prescriptions regarding polypharmacy. Polypharmacy is considered as prescribing and consuming drugs more than necessary [32]. Moradi, Modarres, and Sepehri [32] applied two types of decision trees method to generate a set of if-then rules. Their results demonstrated the capabilities of the data mining framework in the detection and analysis of polypharmacy.

As apropos of infertility treatment, Figueira et al. [4] developed a tool that suggests the number of transferred embryos using sorting techniques. Naser and Alhabbash [33] carried out a study on male infertility and proposed an expert system that diagnosed the disease based on the collected information and suggested a suitable treatment. DeSouza, Jacob [34] investigates the possibilities of proposing a decision support system for infertility decision-making and showed that some factors like endometriosis, psychosomatic, and cervical were statistically associated with the final diagnoses. DeSouza, Jacob [34] concluded that infertility clinical decision support system tends to present more false-positive than false-negatives, whereas the expert physician tends to present more false-negatives so, the decision support system and doctor seem to complement each other. Letterie, MacDonald and Shi [35] proposed a decision support system for the management of decision of ovarian stimulation during IVF. They have shown that their proposed predictive analytic algorithm is highly accurate and in agreement with evidence-based decisions by expert teams during ovarian stimulation and IVF. They claimed that their proposed algorithm optimizes clinical decision-making during IVF.

As mentioned above, various studies have introduced clinical decision support systems for infertility treatment. According to our literature review, in none of the studies a decision support system was proposed for ICSI to recommend the suitable treatment protocol and the protocol's success rate. Hence, the present study is an attempt to investigate if a decision support system can be proposed for recommending the suitable protocol for ICSI and estimating its success rate based on the infertility data in the hospital databases and data mining methods.

Neophyte clinicians rely largely on hypothetical deductive reasoning to solve problems, In other words, they apply knowledge of the relationships between signs, symptoms, and pathophysiology of disease to diagnose and treat problems [36]. Whereas, veterans employ pattern recognition to a greater extent, and reserve analytical approaches for complex cases [37, 38] and according to DeSouza, Jacob [34], decision support systems and doctors seem to complement each other. In addition, such a system can help inexperienced physicians to crosscheck their decisions, to improve precision and appropriateness, by distilling multi-dimensional information from previous instances. This system can also improve the speed and reliability of the treatment because obviates the need to consult many non-thematically organized previous cases.

This paper is organized as follows. Section two presents the details of the proposed system. The results of the proposed system fed with the data and its efficiency are discussed in section three, and the paper is concluded with the conclusions section.

2. Research design

The decision support systems use data and models to solve problems [39]. These systems are composed of a database, model base, and software system components that connect the user to each component [39]. The proposed framework which is depicted in Figure 1, is based on the general architecture of decision support systems and thus, it is composed of the preparation and recommendation phases and the user interface.

2.1. Preparation phase

2.1.1. Feature selection and data cleansing

In the preparation phase, initially, the most effective features in ICSI are extracted. In this research, these features were selected based on expert opinions including *fertility doctors* and *infertility specialists* (Table 1). Having the key features selected, the data is cleansed. Afterward, the data should be normalized to nullify the diluting effect of varying intervals. In this research, the data is normalized using the min-max approach. Finally, the normalized and cleansed data is stored in the system database.

2.2. Recommendation phase

The recommendation phase consists of the model base, success rate computation, and evaluation modules. In the model base module, supervised learning algorithms including logistic regression, decision tree methods, and support vector machines (SVMs) are employed and the performance of each is evaluated in terms of accuracy, precision, and recall. These values will be used in the evaluation module to compare the classifiers.

Then, the success rate of the recommended protocol is calculated based on the historical data, extant in the success rate computation module which is used in the protocol recommendation and success rate modules.

2.2.1. Model base module

Since the output variable, i.e., kind of protocol, in this research is categorical and the label values of it are defined (i.e., short, long, pure), the classification methods can be utilized to predict the outcome variable. This research draws upon logistic regression, SVM, and decision tree to predict the outcome variable because, on the one hand, the outcome variable is categorical, and on the other hand, logistic regression, SVM, and decision tree methods are among the most effective classification methods [40].

Logistic regression is a multiple regression approach whose response variable is of categorical type [41]. In logistic regression, unlike standard regression, the value of the output variable is not predicted, rather the likelihood of the occurrence of different levels of the output variable is predicted. Accordingly, the research problem can be defined as equation 1.1.

$$P(kind\_of\_protocol) = 1 \Big/ \left(1 + e^{(-(b_0 + b_1 TF + b_2 OF + b_3 MF + b_4 Age + b_5 BMI + b_6 Infertility + b_7 Duration + b_8 FSH + b_9 LH + b_{10} Estradiol + b_{11} Tickness))}\right) \tag{1.1}$$

Decision tree methods, including Reduces Error Pruning (REP) tree, random tree, Logistic Model Tree (LMT), and random forest, can be defined by a set of if-then rules. REP tree classifier builds a decision/regression tree by computing information gain/variance and applies reduced-error pruning on it. This algorithm can deal with missing values in the data by splitting the corresponding instances into pieces. The random tree method constructs a tree that considers k randomly chosen features at each node.

LMT is a supervised learning algorithm that combines logistic regression and decision trees. It uses a stepwise fitting process to construct the logistic regression models which can select relevant features in the data. It can also deal with multi-class variables and missing values.

Random forest, as another decision tree method, constructs a forest of random trees based on the training set. As common with any supervised learning method, the random forest should secede what class label to be assigned to the new instances. In order to do so, this algorithm allocates the new instance to every single tree and checks if the instance can pass the truth conditions of the branches within each tree, and as a result, the instance is assigned a class label. Having assigned a class label from each tree, the instance will be assigned the ultimate class label through a vote counting procedure. In other words, the forest chooses the label value which is most frequent. Random forest runs efficiently on large datasets and can handle thousands of features. It can also deal with missing values, maintaining accuracy even if a large portion of data is missing.

Support vector machines (SVMs) are able to classify the data linearly and nonlinearly by different kernels. SVMs are widely used in many programs due to their considerable robust performance against diverse and noisy data [42]. In this method, the hyper-plane maximizes the distance between data that has different class labels.

2.2.2. Evaluation module

In the evaluation module, the classifiers are compared in terms of accuracy, precision, and recall. Accuracy is the ratio of the instances predicted correctly, including both the true positives and the true negatives, to the total number of the instances, as formulized below in equation 1.2:

$$accuracy = \frac{true\_positive + true\_negative}{total\_ins\tan ces} \tag{1.2}$$

The recall is the ratio of the number of instances put correctly into a suitable protocol class to the total number of instances that in actuality exist in that given class [42], as depicted in the formula 1.3.

$$recall = \frac{true\_positive}{total\_positive} \tag{1.3}$$

Precision refers to the ratio of correctly predicted instances to the sum of the instances in that class, as shown in the formula 1.4. In this formula, a false positive is the number of instances put inaccurately in that class [42].

$$precision = \frac{true\_posotive}{true\_posotive + false\_positive} \tag{1.4}$$

Based on these criteria, the best classifier is selected, and the result is returned to the model base module to send the proposed protocol to the success rate computation module so as to calculate the success of the recommended protocol.

2.2.3. Success rate computation module

In this module, the feature values of chemical outcome, either 1 or 0, which respectively shows the positive or negative result of the laboratory fertility test, as well as the feature values of the clinical outcome, either 1 or 0, respectively suggesting successful or failed delivery, will be used to calculate the average success rate of the treatment protocol. This procedure is represented in the following pseudo-code (Figure 2).

2.2.4. **Reporting the Proposed Protocol and the Success Rate**

In this module, the proposed treatment protocol code, namely, two, three, or four, which is recommended by the model base module is converted into its name, respectively, short, long, or pure and subsequently, the name and success rate of the protocol are reported to the user.

3. Experimental results

In this research, anonymous summary reports from the infertility database of a Hospital in Tehran, Iran, including 702 cases were used as the data source. Following the cleansing phase, including missing data removal and normalization, 674 high-quality data records, or the digital summary of medical cases, were obtained. To meet the ethical requirements and to protect the privacy of the patients, the research ethics committee of the hospital led by the dean of hospital approved the research and the fieldwork. Accordingly, the data were completely anonymized and all the sensitive information was removed before being given to the researchers. Moreover, the hospital, in compliance with the approval of the ethics committee, only reported the summary of the data. Simply put, the full medical cases were not revealed and only the data related to the fourteen solicited variables, represented in the first column of Table 2 and 3, were reported to the researchers.

Table 2 shows the distribution data for the categorical variables, and Table 3 contains the descriptive statistics for the interval variables.

In order to assess the performance of the proposed decision support system, 10-fold cross-validation was used not only because it uses all the cases both as the training set and the test set, but also because it does not rely on how the data is divided. 10-fold cross-validation divides the dataset into 10 subsets and the holdout method is repeated 10 times for each of them. Each time, 9 subsets are used as training set and one subset forms the test set. In other words, every subset is used once as a test set, while the remaining subsets form the training set and the error is calculated for each trial. In the end, the average error across all 10 trials is computed.

3.2. Results

As stated in section 2.2.2, the evaluation module compares the performance of different classification methods in terms of accuracy, precision, and recall and based on the results of these comparisons, the best method is selected. The best method is fed into the model-based module to decide upon the proposed treatment protocol, either short, long, or pure. The treatment protocol is sent to the success rate computation, and finally, the proposed protocol and the success rate are reported. Given this procedure, it can evidently be understood that the performance of the best method reflects the performance of the proposed system because it acts, in one way or another, as the core of the other modules.

Table 4 represents the accuracy, precision, and recall criteria of different classification methods, as introduced in section 2.2.1.

As shown in Table 4 and Figures 3 and 4, the random forest (with 6 trees) outperformed the other classification methods with an average accuracy, precision, and recall of 89.76%, 89.5%, and 89.8%, respectively. These statistics also suggest that a decision support system based on random forest can recommend the most reliable solutions.

4. Discussion

The increased use of information storage tools in hospitals has led to the creation of large volumes of data that can be utilized to develop medical decision support systems, such as the infertility decision support system. These systems can offer informed recommendations about the number of transferred embryos, visualization of the data on the polycystic ovary syndrome, diagnosis of disease types, and the treatments for male infertility. Since almost no study, to date, has been conducted on the systems for recommending a suitable ICSI treatment protocol and its success rate, the physicians and medical specialists are deprived of the help of the smart scientific aid applications, to cross-validate their decisions, and have to rely solely on their own experience and knowledge which might sometimes be susceptible to inadvertent inaccuracies or the inevitable human bias factors. This study suggested guidelines for the development of a computerized system based on data mining methods that can propose the suitable infertility treatment protocol with its success rate to help medical specialists, especially the less experienced ones, cross-validate their decisions and prescriptions.

Hence, the data on 11 features recommended by the *fertility doctors* and *infertility specialists were collected from a* hospital database, with the ethics approval sustained. These data were used to devise a decision support system based on the classification methods to make an informed suggestion about suitable infertility treatment protocols. For this purpose, the performance of different classification methods was compared and it was found that the random forest method (with the number of trees equal to 6) excels the others, so the system was based upon it. Although the evaluation of this system showed satisfactory accuracy and precision, the recall criterion had a marginal value. This was probably due to the number of imbalanced data items in different protocols, so future research should tap into this issue. The results from this research also indicated that the decision support systems are capable of recommending suitable treatment protocols for ICSI if they are provided with satisfactory data. Therefore, these systems combined with novice physicians can increase the precision of decisions.

5. Limitations and future studies

This study has used the dataset of only one hospital. While to assure the performance and generalizability of the proposed system, it is suggested that the study is replicated with other datasets in different contexts.

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Figures and tables captions:

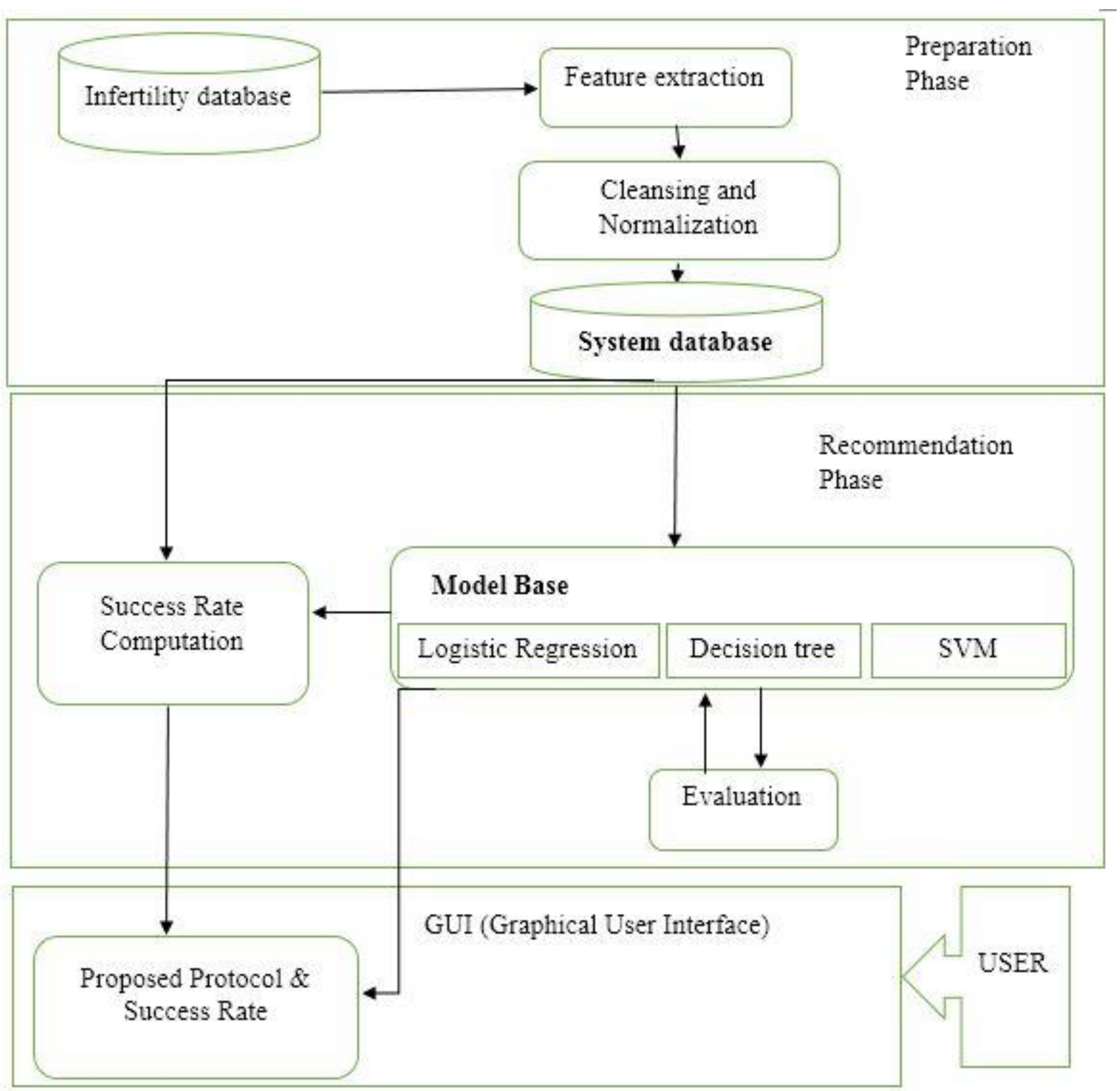


Figure 1.

Table1.

Feature	**Type**	**Description**	**Values**
TF	Categorical	Infertility factor (Tubal Factor)	1: positive 2: negative
OF	Categorical	Infertility factor (Ovarian Factor)	1: positive 2: negative
MF	Categorical	Infertility factor (Male Factor)	1: positive 2: negative
Age	Numerical	Woman's age is computed based on date of birth	Continuous
BMI	Numerical	Body Mass Index	Continuous
Infertility	Categorical	Type of infertility (primary/ secondary)	1: primary 2: secondary
Duration	Numerical	Infertility duration	Continues=>1
FSH	Numerical	Female Hormonal Test (FSH)	Continuous
LH	Numerical	Female Hormonal Test (LH)	Continuous
Estradiol	Numerical	Female Hormonal Test (Estradiol)	Continuous
Thickness	Numerical	Thickness of endometrium	Continuous
Outcome CLN	Categorical	Clinical outcome of used protocol	0: fail 1: success
Outcome CHM	Categorical	Chemical outcome of used protocol	0: fail 1: success
Outcome Negative	Categorical	The outcome of investigating the usefulness of protocol in chemical and clinical modes	0: useful 1: not useful
Kind of Protocol	Categorical (target)	Common protocols in ICSI	1: short 2: long 3: pure

```
procedure success_rateProtocolCHM()
{
categorize the data based on KindofProtocol field;
for each category
   {
     count the total number of data in outcome CHM and store it in variable totalCHM;
     count the instances with value equal 1 in outcome CHM and store it in variable succCHM;
     successCHM_percentage= (succ/total)*100;
   }
}
procedure success_rateProtocolCL()
{
categorize the data based on KindofProtocol field;
for each category
   {
     count the total number of data in outcome CL and store it in variable totalCL;
     count the instances with value equal 1 in outcome CL and store it in variable succCL;
     successCL_percentage= (succ/total)*100;
   }
}
```

Figure 2.

Table 2.

Feature	Number of cases
TF	Category with label 1=541 Category with label 2=133
OF	Category with label 1=476 Category with label 2=198
MF	Category with label 1=46 Category with label 2=628
Infertility	Primary=541 Secondary=133
Kind of Protocol	Short=551 Long=87 Pure=36
Outcome clinical	Success category=60 Failed category=614
Outcome chemical	Success category=77 Failed category=597

Table 3.

Feature	Mean	Min	Max
Age	31.81	20	51
BMI	25.30	14.17	44.98
Duration	7.74	1	30
FSH	5.28	0.10	76

LH	8.80	0.10	101
Estradiol	86.53	0.60	673
Thickness	9.29	4.00	17

Table 4.

Classifier	Accuracy	Precision	Recall
Logistic Regression	81.8991%	0.703	0.819
Decision Trees			
REP Tree	82.1958%	0.782	0.822
Random Tree	89.0208%	0.889	0.890
Random Forest	**89.7626%**	**0.895**	**0.898**
LMT	85.7567%	0.847	0.858
SVM			
SVM (RBF kernel)	81.7507%	0.668	0.818
SVM (Polynomial kernel)	81.7507%	0.668	0.818

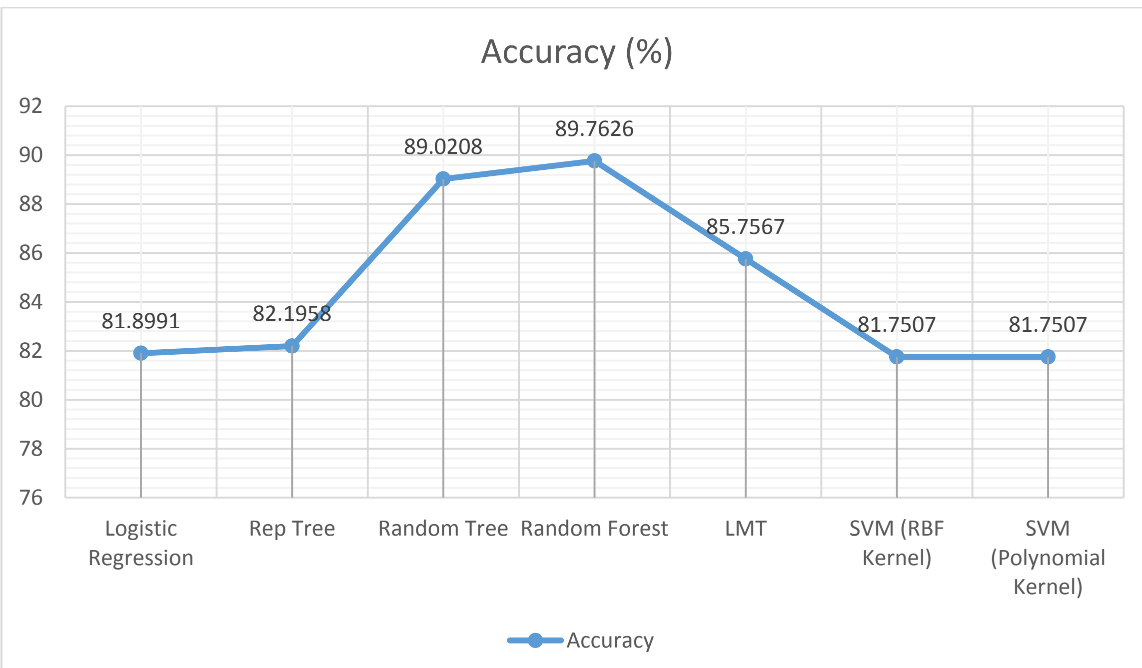
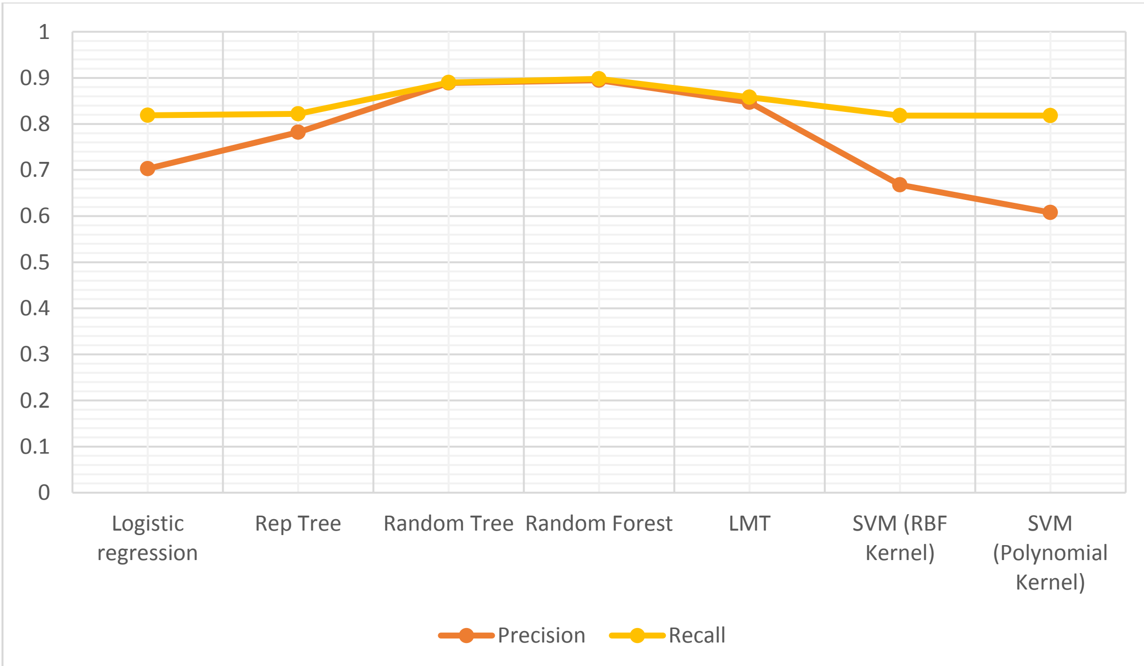


Figure 3.



1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Logistic regression
Rep Tree
Random Tree
Random Forest
LMT
SVM (RBF Kernel)
SVM (Polynomial Kernel)
Precision
Recall

Figure 4.