

A Review of Machine Learning Approaches in Assisted Reproductive Technologies

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doi: 10.5455/aim.2019.27.205-211

ACTA INFORM MED. 2019 SEP 27(3): 205-211

Received: Jul 05, 2019 • Accepted: Aug 12, 2019

ABSTRACT

Introduction: Assisted reproductive technologies (ART) are recent improvements in infertility treatment. However, there is no significant increase in pregnancy rates with the aid of ART. Costly and complex process of ART's makes them as challenging issues. Computational prediction models could predict treatment outcome, before the start of an ART cycle. **Aim:** This review provides an overview on machine learning-based prediction models in ART. **Methods:** This article was executed based on a literature review through scientific databases search such as PubMed, Scopus, Web of Science and Google Scholar. **Results:** We identified 20 papers reporting on machine learning-based prediction models in IVF or ICSI settings. All of the models were validated only by internal validation. Therefore, external validation of the models and the impact analysis of them were the missing parts of the all studies. **Conclusion:** Machine learning-based prediction models provide a clinical decision support tool for both clinicians and patients and lead to improvement in ART success rates.

Keywords: Assisted reproductive technology (ART), infertility, machine learning, computational algorithms, prediction model.

1. INTRODUCTION

Infertility is defined as failure to achieve pregnancy after 12 months of unprotected intercourse (1). According to the World Health Organization (WHO), "infertility is a disease which generates disability as an impairment of function" (2). Infertility affects more than 186 million couples in worldwide that majority of them are deprived of proper treatments in developing countries. So, infertility is known as a most common global health problem (3). There are various types of approaches for conducting the infertility treatment, such as lifestyle changes, drug therapy, surgical methods and assisted reproductive technologies (ART) (4). ARTs are advanced technologies but overall success rate of the ART's is less than 30% (5). ART includes multiple stages that are complex, time-consuming (more than approximately two weeks), expensive and frustrating for infertile couples (6, 7). Opposite to general perception, ART does not guarantee the success. Despite the multiple ART cycles, 38-49% of couples remain in-

fertile (8). Therefore, it is necessary that infertile couples should be well informed about their probability of success. Families should decide on ART as a treatment with considering the success chance, financial burden, physical and emotional risks, multiple pregnancies and complex process of treatment (7, 8).

Reliable prediction of ART outcome is a significant challenge (9). Clinicians are not able to correctly predict treatment outcome, and there is a weak concordance between them on treatment decisions and pregnancy probability estimation (10).

To overcome these problems and provide accurate patient-specific prediction of pregnancy chances, utilizing from computational prediction models are possible solutions. Clinical prediction models are analytical techniques that discover predictive impact of various related information, and consequently estimate the treatment results with significant confidence level. The prediction models fed with patient's personal parameters and other effective ART

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cycle specific variables (8, 11, 12).

2. AIM

The aim of this study is to provide an overview on available prediction models in ART, using varied features set and different machine learning algorithms. Firstly various types of ART techniques are described and then several steps of predictor development were described. The focus of this study is on the machine learning techniques used in the ART treatment in three phase: (1) various data sets used in ART outcome prediction in terms of clinical characteristics, ART cycle parameters, as well as embryological data, (2) different available machine learning algorithms to constructing a computational model, and (3) prediction models used in the literature for predicting ART outcome. Finally, we conclude key principles that can be used to critically appraise the literature on prediction models in ART.

3. METHODS

This article was executed based on a literature review through electronic scientific databases search such as PubMed, Scopus, Web of Science and Google Scholar. We excluded papers which only abstract of them was available, and published in non-English language. For a structured electronic search, the search strategy was formed using keywords such as, assisted reproductive technology (ART), in vitro fertilization, infertility, machine learning, computational algorithms and prediction models.

4. RESULTS

4.1. ART Techniques

ART procedures defined as human oocytes, sperm and embryo(s) are handled *in vitro* conditions for the purpose of establishing a clinical pregnancy (6). In vitro fertilization (IVF) and intra-cytoplasmic sperm injection (ICSI) are two famous techniques that widely used among ART's, which have nearly the same stages (7). The typical ART treatment cycle usually is like the followings: First, starts with controlled drug-induced ovarian stimulation to produce several mature eggs. To do this, gonadotropins such as human menopausal gonadotropin (HMG) and follicle-stimulating hormone (FSH) are used for ovulatory stimulation in different protocols. Also, human chorionic gonadotropin (HCG) is used as ovulation trigger to stimulate final oocyte maturation for oocyte retrieval. After the oocyte-retrieval from the woman's ovaries, sperm and oocytes are fertilized in vitro. This phase in the ICSI executed by injection a selected sperm into the oocyte cytoplasm. So, ICSI is a right treatment solution in severe male factor infertility, such as azoospermia (13). Later, the resultant embryos are formed and cultured outside the body and developed to cleavage or blastocyst stage. Finally, the viable embryos are chosen and transferred into the woman's uterus (6, 14). This subprocess is called embryo transfer (ET). ET is a most important stage in ART, since the selected embryos is critical for increasing implantation chances. ET comprised of multiple parameters, strategies, techniques that are completely subjective and based on experience of the embryologist (15). All

mentioned aspects, are critical and effective to estimate overall ART success rates (16).

4.2. Computational Techniques

In this section, we argue how to develop prediction models by applying different machine learning and computational techniques on ART, in three phases (Figure 1).

Phase 1: ART Data Set

In order to successful knowledge discovery in databases (KDD), well-defined and formal methods should be applied for managing data. Cross-industry standard process for data mining (CRISP-DM) model is a standard methodology, which includes six phases: 1) problem domain understanding, 2) data understanding, 3) data preparation, 4) modeling, 5) evaluation and 6) deployment (using the discovered knowledge) (17, 18).

The dataset construction is followed by data entry process of medical records and data pre-processing. Data preprocessing is one of the most important steps and critical in the success of machine learning techniques (19). The purpose of this step is to construct the final dataset from original raw data set as optimum input into the modeling algorithms (17).

Data preparation is performed by data cleaning, handling of missing values, outlier data and applying of normalization methods. The missing values of numerical features are replaced with median and nominal attributes are filled by mode of their corresponding feature (20). Preparing of data also completes with feature selection (FS) and ranking algorithms. At this point, after attribute extraction from clinical practice guidelines, papers and experts opinion, by applying FS algorithms the final feature set is building as potential predictors for ART outcome. FS algorithms recruit to identify features that have important predictive role. These techniques do not change the content of initial features set, only select a subset of them. The purpose of feature selection is help to create optimize and cost-benefit models for enhancing prediction performance. There are different FS techniques, such as, filter techniques (Information gain, Gain ratio, etc.) that use to select and rank the optimal number of attributes. These algorithms score each feature, and then based on superior performance of prediction models, low-weighted features are removed (21).

Reporting of potential predictors in the literature without using the same initial feature set and categories, leads to difficult result interpretation and comparison (22). Therefore, in this study we categorize different variables into subgroups (i.e. patient-related clinical and demographics Information, female/male pathology, oocyte stimulation and morphology, semen analysis, embryological data and lab tests) that have contribution on prediction of ART outcome. Table 1, shows characteristics of examined datasets on 20 studies.

All of these studies, except one of them (23), have performed feature selection techniques on their datasets. The age of woman attribute is the most important feature in many (i.e. 9 studies) of machine learning based prediction studies on ART outcome (7, 9, 18, 24-29). The maximum number of features was 64 (12), and the minimum number of features was four (26), which were recruited

in ART predictive modeling studies. Of the all papers on ART prediction model, five papers used more comprehensive features set, according to Table 1 (18, 25, 27, 29, 30).

Phase 2: Predictive Modeling

To develop more accurate prediction models with high-performance capacity, advanced computational techniques and data mining methods could be employed (28). The focus of machine learning and data mining (DM) techniques are on developing computerized and efficient predictive modeling by exploring hidden and unknown patterns in data to discover knowledge with high accuracy. However, conventional statistical methods are fitted to predefined models (11, 28, 39).

The purpose of machine learning is to design and develop prediction models, by allowing the computer learn from data or experience to solve a certain problem (40). Today, there is a growing trend in using of machine learning on vast variety of subjects in health care (41). A practical application of machine learning in medical industry is clinical decision support systems (CDSS), that help to precise designation of treatment plan (42).

There are two major types of machine learning approaches: (i) supervised and (ii) unsupervised learning. In supervised learning, the training data set are labeled. The goal of supervised learning algorithms is to predict the value of target variable. Therefore, supervised learning adjusted for predictive modeling. Most commonly machine learning algorithms which are called classification algorithms are related to this category. Unsupervised learning is used in descriptive modeling and unlabeled data, by detecting underlying patterns with unlabeled data. Clustering and association rules are typically unsupervised learning algorithms.

The most familiar classification algorithms are support vector machines (SVM), neural network (NN), k-nearest neighborhood (kNN), naive bayes (NB), random forest (RF) and decision tree (DT) which are commonly used to develop a prediction models. In the rest of this paper, we will investigate these algorithms in studies related to ART outcome prediction. In spite of the efficiency of the machine learning approaches as computational techniques to predict ART treatment outcome, there are few number of studies in this field (27), Studies with complete aspects of ART data and sufficient number of effective variables are rare (28, 43).

In this study, we provide an overview on prediction models in ART. Our search retrieved 20 studies which are applied supervised machine learning algorithms in IVF or ICSI settings. The characteristics of the prediction models in these papers are summarized in Table 2. Statistical methods are not suitable in prediction of ART outcome (11) then in this paper the statistical approaches are excluded .

Phase 3: Prediction and Evaluation

Model evaluation is an important step in CRISP-DM. At this stage, after prediction model development based on prospective data, the performance of model should be evaluated for unseen data to validate for real-world settings (44). The process of model validation is subdivided into internal and external validation. Internal validation,



Figure 1. Three phases of prediction model development by machine learning techniques

		Predicted Class	
		Positive	Negative
True Class	Positive	TP	FN
	Negative	FP	TN

Figure 2. A simple confusion matrix

which is prior to external validation, refers to the model performance evaluation in the same dataset in which the model was developed. This type of validation leads to excessive optimism about model’s power in outcome predictions. In contrast to this, external validation is evaluation of prediction model in varied population and settings. External validation supports the generalizability and transportability of model. Generalization of a model led to overcome data changes challenges over time, since the model can works in different clinics with adaptation of the clinic-specific characteristics and parameters and easily transfer to many others.

According to Table 2, none of the models for prediction of ART outcome were validated externally. These models only examined with internal validation.

In machine learning methods, the prediction process needs two types of data: training and testing data. Most of the input data (i.e. almost 80% of the data set), is placed in training set and the remaining data is called the test set. Training set is used for model generation and training algorithms, whereas the test set validates it. A standard evaluation method is essential to assess the performance of model. There are different techniques for evaluating the performance of prediction model, such as random sampling, bootstrapping, simple split (holdout) and k-fold cross validation (45). The most commonly used method is k-fold cross validation in studies. In k-fold cross validation (mainly k=10), the dataset is randomly divided into 10 subsets with equal size, and the model is trained and tested 10 times. Each time, one of the 10 subsets is used as the validation set for testing the model and the remaining 9 subsets put together to form a training data set. Finally, 10 results of experiments are averaged to provide a single estimation for model.

There are golden standards of performance evaluation metrics for predictive modeling. In machine learning classification, the basic performance measurement is confusion matrix. This table shows the predicted and actual classes (Figure 2).

Study	No. of records	No. of features	feature selection	Patient-related clinical and demographics Data	Female Pathology Data	Oocyte stimulation and morphology Data	Male Pathology Data	Semen Analysis Data	Embryological Data	Lab Tests	High score feature
Kaufmann et al. (1997) (24)	455	14	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Age
Juristica et al. (1998) (31)	788	55	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	A series of E2 levels
Kim and Jung (2003) (25)	269	8	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Age of female
Passmore et al. (2003) (32)	325	max= 53 min= 6	Yes	Yes	No	Yes	No	No	Yes	Yes	Final FSH dose
Wald et al. (2005) (26)	113	4	Yes	Yes	No	No	Yes	Yes	No	No	Maternal age
Morales et al. (2008) (15)	63	20	Yes	Yes	No	No	No	Yes	Yes	No	Embryo blastomere size
Linda et al. (2008) (33)	152	17	Yes	Yes	No	Yes	No	No	Yes	No	Duration of infertility
Chen et al. (2009) (34)	654	10	Yes	Yes	No	Yes	No	No	Yes	No	Not mentioned.
Nanni et al. (2010) (35)	62	10	Yes	Yes	Yes	No	No	No	No	No	Sub-endometrial VI
Guh et al. (2011) (18)	5275	67	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Age
Corani et al. (2013) (9)	388	7	Yes	Yes	No	No	No	No	Yes	No	Age
Durairaj and Ramasamy (2013) (36)	250	27	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Unexplained factor of Female Pathology
Malinowski et al. (2013) (23)	1995	26	No	Yes	Yes	Yes	No	Yes	Yes	Yes	None
Uyar et al. (2014) (27)	3898	18	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Age of female
Güvenir et al. (2015) (12)	1456	64	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Laparoscopic Surgery
Chen et al. (2016) (28)	871	13	Yes	Yes	Yes	No	Yes	No	Yes	No	Maternal age
Mirroshandel et al. (2016) (37)*	219	1) 13 2) 14 3) 15	Yes	Yes	No	No	Yes	Yes	Yes	Yes	1) FSH 2) 2PN Degree 3) Embryo Degree
Hafiz et al. (2017) (7)	486	29	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Age of female
Blank et al. (2018) (30)	1052	32	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Gravidity
Hassan et al. (2018) (29)	1048	25	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Age

Table 1. Description of examined datasets in the literature. * This study presented prediction models on three targets: 1) 2PN degree prediction, 2) Embryo quality prediction, and 3) Pregnancy prediction.

The most common standard machine learning evaluation parameters are computed based on the values of true negatives (TN), true positives (TP), false positives (FP),

and false negatives (FN) as detailed below.

Accuracy (ACC): percentage of positive and negative class correctly predicted:

Study	Technique(s)	ART method	Target (outcome)	External validation
Kaufmann et al. (1997)	Artificial Neural Networks (ANN)	IVF	Pregnancy	No
Juristica et al. (1998)	Case-based reasoning (CBR)	IVF	Pregnancy	No
Kim and Jung (2003)	Bayesian network	IVF	Pregnancy	No
Passmore et al. (2003)	C5.0 Decision Tree	IVF	Pregnancy	No
Wald et al. (2005)	4-hidden node neural network	ICSI/IVF	intrauterine pregnancy	No
Morales et al. (2008)	Bayesian classification	IVF	Embryo implantation	No
Linda et al. (2009)	Bayesian network	IVF	ongoing pregnancy	No
Chen et al. (2009)	PSO, Decision Tree J48, Naïve Bayes, Bayes Net, MLP ANN	ICSI/IVF	Pregnancy	No
Nanni et al. (2010)	SVM, NN, DT	ICSI	Pregnancy	No
Guh et al. (2011)	genetic algorithm and decision tree	ICSI	Pregnancy	No
Corani et al. (2013)	Bayesian network	IVF	Pregnancy	No
Durairaj and Ramasamy (2013)	MLP ANN	IVF	pregnancy	No
Malinowski et al. (2013)	ANN	IVF/ICSI	Pregnancy	No
Uyar et al. (2014)	NB, KNN, SVM, DT, MLP, radial basis function network	IVF/ICSI	Implantation	No
Güvenir et al. (2015)	NB and RF	IVF	clinical pregnancy	No
Chen et al. (2016)	multivariable logistic regression (LR) and multivariate adaptive regression splines (MARS)	IVF/ICSI	clinical pregnancy	No
Mirroshandel et al. (2016)	NB, SVM, MLP, IBK, KStar, Bagging (KStar), RandomCommittee, J48, RF	ICSI	1) 2PN degree prediction 2) Embryo quality prediction 3) Clinical pregnancy (Beta test) prediction	No
Hafiz et al. (2017)	SVM, RPART, RF, Adaboost, 1NN	IVF/ICSI	Implantation	No
Blank et al. (2018)	RF	IVF/ ICSI	Ongoing pregnancy	No
Hassan et al. (2018)	MLP, SVM, C4.5, CART, RF	IVF	pregnancy	No

Table 2. The characteristics of machine learning–based prediction models on ART.

$$NPV = \frac{TN}{(TN + FN)} \times 100$$

Sensitivity (SN): percentage of positive class that were predicted correctly:

$$NPV = \frac{TN}{(TN + FN)} \times 100$$

Specificity (SP): percentage of negative class that were correctly predicted:

$$NPV = \frac{TN}{(TN + FN)} \times 100$$

Matthews Correlation Coefficient (MCC): this value ranges from -1 for worst prediction to +1 for accurate prediction; zero indicates random prediction:

$$NPV = \frac{TN}{(TN + FN)} \times 100$$

Precision or positive predictive value (PPV):

$$NPV = \frac{TN}{(TN + FN)} \times 100$$

Negative predictive value (NPV):

$$NPV = \frac{TN}{(TN + FN)} \times 100$$

F-measure: this parameter is a combined evaluation of precision and recall:

$$F_score = \frac{Precision \times Recall}{Precision + Recall} \times 100$$

Area under the curve (AUC): this parameter is a logical evaluation for model performance. Its value ranges from 0 to 1, where 1 represents the best performance and 0 is the worst performance. AUC = 0.5 when random ranking is used.

The area under the ROC curve (AUC), has a pivotal role in evaluating prediction models and is a reliable and

popular performance measure for assessing the quality of classification algorithms in the machine learning methods (12). The high value of AUC shows the reliability of prediction model.

5. CONCLUSION

The application of computational approaches, i.e. machine learning-based prediction models, can increase pregnancy rate after ART treatments. Also, these intelligent models have a promising benefit in the presentation of a clinical decision support tool to clinicians and infertile couples to be well informed about the chances of success before the treatment procedure. Therefore, the survey of exist models in the prediction of ART outcome is essential to identify the impact of them in real world settings. This study addressed this issue through the step by step consideration of prediction models development phases. In this review, we identified 20 prediction models in ART treatments. External validation of the model was the missing part of the all studies. Thus, the impacts of them have not yet been analyzed for any of applications. As a future work, we encourage further upgrading of these existing prediction models on efficient datasets from various infertility clinics, as well as supporting the possibility and advantages of them by conducting randomized clinical trials.

- **Acknowledgments:** This research was a part of an MSc thesis that approved by Tabriz University of Medical Sciences.
- **Authors contribution:** Both authors have contributed to writing the article and approving the final manuscript.
- **Conflict of interest:** The authors declare no conflict of interest.
- **Financial support:** This research was funded by Tabriz University of Medical Sciences

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