Biochemical Markers as Predictors of IVF Success: A Machine Learning Approach

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The success of in vitro fertilization (IVF) treatments is influenced by a complex interplay of multiple factors, including patient-specific biochemical parameters. In this study, a machine learning approach is used to analyze the biochemical markers of the patient undergoing IVF. A dataset of 28 patients undergoing IVF treatments was collected, comprising a range of 21 biochemical parameters. Traditional logistic regression, support vector machines, decision trees and random forests classification were applied to analyze and model the data. The feature selection and dimensionality reduction techniques has been used to identify the most relevant and informative markers for IVF prediction. Subsequently, the various sets of selected marker values have been used to train and predict IVF success outcomes, and to evaluate performance of classification models in terms of accuracy, sensitivity, and specificity depending on the selected markers or features. The results have shown that it is possible to formulate a certain probability of IVF based on these markers, and that most of the used classification models required a smaller number of markers. As for the performance, the best results were achieved by the SVM and decision trees approaches, which achieved 70-80 % prediction accuracy using several parameters less than 6.
Keywords: in vitro fertilization, machine learning, binary classification

Aplikácia strojového učenia pri analýze biochemických parametrov z pohľadu predikcie úspešnosti IVF liečby
Úspešnosť IVF liečby je ovplyvnená komplexnou súhrou faktorov vrátane biochemických parametrov špecifických pre pacienta. V tejto štúdii sa analyzovalo 21 biochemických markerov séra 28 pacientov podstupujúcich IVF pomocou strojového učenia. Na analýzu a modelovanie údajov bola použitá tradičná logistická regresia, metóda podporných vektorových strojov, metóda rozhodovacích stromov a metóda náhodných lesov. Na identifikáciu najsignifikantnejších a informatívnych markerov na predpovedanie IVF sa použili techniky výberu príznakov a redukcie dimenzie dát. Následne sa rôzne súbory hodnôt vybraných markerov použili na trénovanie a predpovedanie výsledkov IVF a na vyhodnotenie výkonnosti klasifikačných modelov z hľadiska presnosti, citlivosti a špecifickosti v závislosti od vybraných markerov alebo znakov. Výsledky ukázali, že na základe týchto markerov je možné formulovať určitú pravdepodobnosť IVF úspešnosti, pričom väčšina použitých klasifikačných modelov vyžadovala menší počet markerov, ako bolo vo vstupnej dátovej množine. V súvislosti s výkonnosťou dosiahla najlepšie výsledky metóda SVM a metóda rozhodovacích stromov, ktoré nadobudli presnosť predpovedí v rozmedzí 70 – 80 % pri použití menej ako 6 biochemických parametrov.
Kľúčové slová: in vitro fertilizácia, strojové učenie, binárna klasifikácia

Introduction

In vitro fertilization (IVF) is a widely used assisted reproductive technology that aims to help infertile couples conceive[1]. However, the success rate of IVF is low and varies depending on numerous factors, such as the quality of oocytes, sperm, embryos, and the endometrium[2]. Therefore, there is a need for reliable methods to predict the outcome of IVF and improve its efficiency. One of the possible methods is to analyze the biochemical parameters of the patient undergoing IVF[3]. However, the analysis of the biochemical parameters is challenging, as they are influenced by many factors, such as age, body mass index, lifestyle, and medication of the patients. Moreover, the biochemical parameters are often correlated with each other, and their individual effects on the IVF outcome are difficult to isolate[4]. Therefore, a machine learning approach is needed to handle the complexity and the

high dimensionality of data types, and to identify the most relevant and informative markers for IVF prediction[5]. Machine learning is a branch of artificial intelligence that uses algorithms to learn from data and make predictions or decisions. Machine learning can be applied to various types of data, such as numerical, categorical, textual, or image data, and can perform various tasks, such as classification, regression, clustering, or recommendation[6].

There are studies in the literature that show how machine learning can be used to predict the outcome of IVF using different combinations of various parameters collected at various stages of process and of various type[7,8]. In this study, a machine learning approach was used to analyze solely the set of biochemical parameters of the patient undergoing IVF, and to classify them into pregnant or non-pregnant groups based on their biochemical profiles. The traditional logistic

regression, support vector machines, decision trees and random forests classification methods have been applied to analyze and model the data. To estimate an importance of biochemical parameters, feature selection and dimensionality reduction techniques was applied to identify the most relevant and informative feature markers for IVF prediction. The various sets of selected marker values were then utilized to train and predict IVF success outcomes, and to evaluate the performance of the classification models in terms of accuracy, sensitivity, and specificity depending on the selected markers or features. The results of the different machine learning approaches, and their implications for IVF decision making and counseling are discussed.

Materials and Methods

The study used a dataset consisting of 21 biochemical parameters obtained from 28 patients on the day of egg transfer. The patients' age and body mass index were also considered, making 23 input parameters in total. Out of the 28 patients, 13 achieved successful IVF outcome and 15 did not.

The input parameters were processed using classical statistical analysis and the mean ± standard deviation values were determined for each parameter. The correlation and possible statistically significant differences were determined by Pearson's chi-square test and parametric Student's t-test. P value < 0.05 was considered as threshold for statistical significance.

To predict the success of the IVF process, four machine learning methods were used - logistic regression (LR), support vector machines (SVM), decision trees (DT), and random forests (RF). For each method, dataset was ran-

domly divided into the training set (70 %), and the test set (30 %).

To analyze the impact of individual input parameters on the prediction, models were trained with different selections of parameters, and thus feature vectors of varying size. The parameter selection was performed using the Recursive Feature Elimination method (REF), which can determine the ranking of parameters according to their significance for the classifier accuracy used in the study[9]. For each classification method, feature vectors of different sizes from 1 to 10 were successively selected using RFE, and a corresponding model was trained for each feature vector. For each trained model, the accuracy, sensitivity, and specificity were determined.

The data processing, model training, and analysis were performed using python and scikit library.

Results

For the statistical analysis, the dataset was split into two groups based on the success or failure of egg transfer. **Table 1** shows the summary of the parameters with their mean values. Comparison of the groups and statistical testing with a t-test and Pearson's chi-square test did not differ significantly in any parameters.

Classification models were trained first with all parameters. The predictive ability of these models was very low (prediction accuracy below 20 %). In the next step, subsets of parameters were selected for training, gradually from 1 to 10 parameters. Which parameter should be included in the set was determined by its ranking by the RFE method. For each classification algorithm, and for each set a model was trained and the prediction accuracy of this model was determi-

Table 1. List of all parameters used in study. The total number of patients were 28, 15 with negative IVF outcome and 13 with positive IVF outcome.

Parameter	Label	Negative (mean ± std)	Positive (mean ± std)
Age	AGE	36.73 ± 4.61	37.31 ± 4.50
Body Mass Index	BMI	24.56 ± 5.61	26.11 ± 5.07
Serum glucose (mmol/l)	S-Glu	5.32 ± 1.05	4.98 ± 0.89
Homocysteine in plasma (umol/l)	P-HCY	10.07 ± 2.63	10.57 ± 3.45
TSH (mIU/l)	TSH	2.87 ± 2.38	1.62 ± 0.86
T4 free in serum (pmol/l)	S-fT4	15.19 ± 4.01	16.79 ± 1.28
aTG (kIU/l)	S-aTG	69.37 ± 103.91	15.14 ± 4.50
aTPO (kIU/l)	S-aTPO	109.14 ± 182.74	43.65 ± 111.61
DHEA-sulfate in serum (umol/l)	S-DHEAS	4.10 ± 2.66	4.06 ± 2.60
Serum testosterone (nmol/l)	S-TST	0.56 ± 0.47	0.46 ± 0.46
Free testosterone (pmol/l)	S-fTST	2.45 ± 1.82	2.47 ± 1.56
SHBG (nmol/l)	S-SHBG	117.20 ± 53.48	97.92 ± 59.20
Ratio TST/SHBG (%)	FAI	0.73 ± 1.36	0.71 ± 0.96
Serum progesterone (nmol/l)	S-PROG	112.43 ± 38.87	110.67 ± 31.73
Serum prolactin (ug/l)	S-PRL	11.14 ± 5.79	15.52 ± 8.64
Serum FSH (IU/l)	S-FSH	2.52 ± 1.40	2.37 ± 1.22
Anti-Mullerian hormone (ug/l)	AMH	3.01 ± 3.73	2.68 ± 3.11
LH (IU/l)	S-LH	3.70 ± 2.85	4.69 ± 3.91
Serum estradiol (pmol/l)	S-E2	848.43 ± 536.98	664.58 ± 362.79
17-OH-progesterone in serum (nmol/l)	S-HPRO	6.30 ± 2.50	5.83 ± 2.09
Serum insulin (mIU/l)	S-Inz	21.84 ± 26.08	24.79 ± 15.67
Vitamin D Total	S-vit. D	32.97 ± 9.11	34.54 ± 10.28
Insulin resistance	HOMA	5.48 ± 6.95	6.24 ± 4.37

Graph 1. Accuracy of predictions of four classification models (LR, SVM, DT and RF) trained with different sized feature sets (Feature Vector).
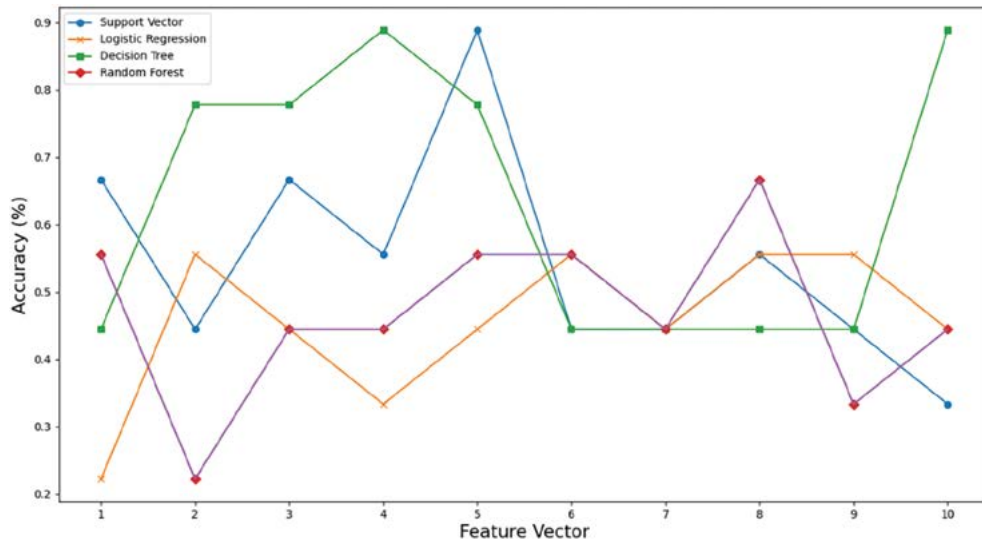
ned. The dependency of accuracy on size of selected sets of parameters is shown on **Graph 1**. Sets of parameters determined by the RFE method differed for individual classification algorithms, and no significant trend was shown in the selection. **Table 2** shows feature vectors for each classification algorithm for which maximum prediction accuracy was achieved.

Discussion

The study focused on the possibility of applying machine learning methods to predict the IVF outcome from biochemical parameters of patients on the day of egg transfer. Four machine learning methods were used - logistic regression, support vector machines, decision trees, and random forests. These methods were reported as convenient choice to build prediction models for IVF outcomes considering various number of clinical parameters (features)[10,11]. This study demonstrated that the methods mentioned can predict IVF outcomes using only biochemical parameters. However, the prediction accuracy differs among techniques and is influenced by the number of parameters used. The SVM and DT methods achieved the highest score by using 5 and 4 parameters, respectively. The remaining two methods RL and RF showed overall low prediction accuracy across of all selected feature sets. However, the reliability of the prediction needs to be carefully discussed. The present study's prediction accuracy is limited due to the scarcity of data, which significantly decreased the precision of all the methods used. Parameters such as age and BMI, for example, were

shown to be insignificantly associated, which contrasts with works that highlight their significance[8,12]. This fact may be explained by the limited amount and structure of the data, where the variability of these two parameters did not exhibit a significant impact on predictive ability. The presented results basically show that it is technically possible to create predictions based on biochemical parameters. The essentially indirect dependence of accuracy and number of characters, as seen on **Graph 1**, points out that even a large number of biochemical parameters can have a limited impact on the predictive performance of classification, because the trend in the data is captured only with a smaller limited number of parameters[12]. In addition, no relationship was demonstrated between the selection of a smaller set of parameters and used different classification methods, what may indicate that considering only biochemical parameters is not sufficient to make a reliable prediction as there is a lack of some significant markers featuring potential prediction-making patterns in patient 's data. This fact suggests that solely biochemical parameters can have limited role in building effective predictors in future work and predictors with more diverse inputs are needed.

Conclusion

Machine learning methods can be applied to the analysis of biochemical markers of IVF patients with a focus on the pure prediction of the success of egg transfer, but for a robust prediction it is not sufficient, and it is necessary to include other diagnostic parameters.

Table 2. The feature vectors (or subset of input biochemical parameters) for that particular classification method have achieved the highest accuracy of prediction of IVF outcome. The name of particular feature corresponds to name from Table 1.

Classifier	Feature Vector	Accuracy	Sensitivity	Specificity
Support Vector	TSH | S-fTST | FAI | S-PRL | S-HPRO	89 %	67 %	83 %
Logistic Regression	TSH | FAI	56 %	50 %	60 %
Decision Tree	S-PRL | AMH | S-LH | S-E2	0.89 %	67 %	83 %
Random Forest	TSH | S-fT4 | S-aTG | S-aTPO | S-SHBG | S-PRL | S-E2 | S-In	0.67 %	60 %	75 %

Data availability statement

All collected and used data adhered to both Slovak national data protection regulations and the European General Data Protection Regulation (GDPR). Any patient-related information has been anonymized to ensure confidentiality.

Ethics statement

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethical committee of Košice Self-Governing District under the identifier 5259/2022/ODDZ-16668 from April 26, 2022. All patients have filled in the questionnaires with relevant information regarding their health status and signed informed consent.

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