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The Prediction of Complications of Blood Transfusion in Thalassemia Patients Using Deep Learning Method

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Abstract

Background and Objective: Thalassemia is the acute hereditary anemia and the most common hemoglobin disorder in the world. The main treatment for this disease is the persistent blood injection, but the injection of blood can have different complications. These complications affect the quality of life of patients and increase the risk of mortality. Moreover, it increases the use of healthcare services and hospital costs. Predicting the risk of complications before blood transfusion, more appropriate alternative treatment can be selected to prevent or reduce the complications. Moreover, identifying high-risk patients and following them after transfusion provides the possibility of timely interventions. So far, several studies have analyzed the effects of blood transfusion and the risk factors of these complications by statistical **method.** However, few studies have attempted to predict these complications. In this study, the risk of post-transfusion complications in thalassemia patients is predicted using machine learning algorithms.
Method: The cross-sectional data were collected from 3489 cases in 12 thalassemia centers in Tehran province and 14 thalassemia centers in Mazandaran province in 2018. A set of different classification models including classic and deep learning techniques were trained and studied on this data set.
Results: The results showed that machine learning methods have good accuracy to predict the risk of post-transfusion complications. According to the results, the deep learning method has improved the results considerably in comparison to other models (precision=0.21, sensitivity=0.77, f1-score=0.33).
Conclusion: In this study, machine learning methods were used to predict the occurrence of post-transfusion complications in thalassemia patients. Finally, the deep learning method produced the best prediction results. Using this method, 77 % of patients who will suffer complications are detected before transfusions. Appropriate alternative methods can be used for treating these patients in order to prevent or reduce transfusion complications.

Keywords: Thalassemia, blood transfusion, complication, prediction, deep learning

Background and Objectives

Every year more than 60,000 babies are born with thalassemia worldwide[1]. Thalassemia is an acute hereditary anemia and the most common hemoglobin disorder in the world. The main treatment of these patients is the persistent blood injection, but the injection of blood can have different complications including allergic reaction, Alloimmunization, iron accumulation and various infections such as hepatitis and HIV. These complications are considered a minor but serious risk in the blood transfusion field. For example, 4717 cases of blood transfusion-related complications across the country have been reported to Hemovigilance Unit of the Blood Transfusion Organization of Iran in 2018[2]. These side effects reduce the quality of life and increase the risk of mortality. Moreover, it increases the use of health care services and hospital costs.

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According to the above considerations, predicting the risk of blood transfusion complications can potentially benefit patients, hospitals and totally health systems. With the identification of patients at risk of blood transfusion complications, more appropriate alternative methods can be selected for treatment. For example, "Yisui Shengxue Granules" (YSSXG), a traditional Chinese medicine used in the treatment of thalassemia patients, is an alternative to the lifelong blood transfusions and iron chelation therapies[3]. It can reduce the complications of blood transfusion in thalassemia patients, such as heart and liver iron accumulation. Moreover, identifying high-risk patients and following them after blood transfusion enables timely interventions[4] .

So far, different studies have been conducted with statistical methods based on the analysis of blood injection complications and risk factors of these complications. But limited studies have been tried to predict the occurrence of these effects[5-7]. For this reason, we used machine learning algorithms in this study to predict the risk of complications after blood transfusions in thalassemia patients. In this regard, a set of different classification models consists of classical methods and a deep learning method were trained and investigated. Finally, the deep learning method produced the best prediction results. Comparing the results showed that deep learning has produced a significant improvement over other models.

In the remainder of this paper, in section 2 the blood injection complications, literature review, and machine learning models are discussed. In section 3 the research data and data preprocessing are presented. Modeling and comparisons and conclusion are presented in sections 4 and 5 respectively.

۱ Related Literature

Complication of blood injection

Blood injection may have some complications. These complications can be classified into 3 groups in terms of their likelihood of prevention[8]

- The reactions that are impossible to prevent such as chronic allergic reactions
- Those that can be prevented by improving working methods such as TA-GVHD that uses irradiated blood.
- Human error reactions that is completely preventable, such as the wrong blood injection.

Table 1 presents the relative frequency of different types of complications approved by Blood Transfusion Organization of Iran in 2018.

Table1- Frequency percentage of an approved type of complications in the year 2018[3]

Type of complication	No.	Relative
Allergic reactions	1819	38.6%
Febrile Non *Hemolytic* Reactions (FNHTR1)	1658	35.1%
Others	656	13.9%
Immune hemolysis-Allo Ab	237	5%
Non immune hemolysis	116	2.5%
Transfusion associated circulatory overload	88	1.9%
Transfusion-associated dyspnea	68	1.4%
Hypotension related to transfusion	48	1%
Immune Hemolysis - ABO mismatch	25	0.5%

According to Table 1, allergic reactions with a relative frequency of 38.6% and Febrile Non-Hemolytic Reactions (FNHTR) with a relative frequency of 35.1% are the most common unpredictable complications following blood injection.

Error due to the wrong injection of blood product constitutes the largest preventable group in reports with ABO incompatibility (0.5%). Some major issues can be prevented by precise supervision and performance improvement. For example, some hemolytic

reactions occur in patients who have hemoglobinopathy and require a red blood cell-free phenotype. Preparation of a compatible RBC unit (k, rh) reduces the risk of increased Allo antibodies in RBC. Various TACO-related fluid overload (TACO) cases can also be prevented by the comprehensive evaluation of blood injection and careful patient monitoring 24 hours after injections.

In this study, we attempted to predict complications that are not caused by human error before injecting thalassemia patients to provide necessary investigations, selected alternative treatment methods, or timely interventions.

Literature review

Due to the importance of reducing complications after blood injection, several studies have been carried out in this field. These studies have mainly investigated the rate of complications of blood injection and the causes of these complications by statistical analysis[1, 9-11]. Another class of papers, reviewed and identified the risk factors for blood injection complications[6, 12-14]. Limited studies have also attempted to predict the likelihood of post-injection complications using machine learning algorithms. Authors of[5] used SparseLDA method so that they were able to predict specificity = 0.72, sensitivity = 0.89, and AUC = 0.84 for predicting transfusion-related acute lung injury (TRALI) and transfusion-associated circulatory overload (TACO). Murphree et al[15]. used treebag ensemble method obtained specificity = 0.71, sensitivity = 0.82 and AUC = 0.83 for TRALI and TACO prediction and concluded that ensemble methods have not enhanced the results of these two complications[7]. used CART algorithm and obtained specificity=0.57 and sensitivity=0.73 for TRALI prediction and specificity=0.56 and sensitivity=0.90 for TACO prediction .

According to our search strategy, no research was found in the literature to predict complications other than TRALI and TACO. Moreover, no paper specifically predicted the complications of blood transfusion in the group of thalassemia patients. In addition, despite the high number of parameters affecting the diagnosis, deep learning method has not been taken into consideration for predicting the complication. Therefore, in this study, in addition to the classical models used in previous research, a deep learning-based model is also presented.

Machine learning

Machine learning is a subset of artificial intelligence that can produce significant results by automating complex data analysis. Machine learning models are trained with a set of data and can be adapted in case of exposing to the new data set. Machine learning algorithms are classified into two main groups: supervised and unsupervised. In the supervised learning method, we use labeled data to train the algorithm. In these scenarios, data is available along with the result and the desired response. In unsupervised learning, there is no target variable, and the purpose is the identification of patterns within data.

In this article, since the complication status of patients is clear, we have to use supervised learning methods. In this regard, various classification models include classical methods were examined. Considering the research background, we selected some of the most used classic models for training including C5.0 decision tree, CART decision tree, random forest, logistic regression, naive Bayesian model, and support vector machine (SVM).

The results of decision trees are interpretable for physicians and the speed of learning of these models is high. Moreover, these models do not need to normalize features. But, decision trees are unable to manage many unrelated features and they are memory intensive.

Random forest does not need normalization either. In addition, it is able to handle missing values and is more accurate. However, this model has a slow learning speed, it is inappropriate for the small number of samples and the results cannot be interpreted.

Logistic regression is capable to model linear problems and it has high speed. But, it is unable to manage many unrelated features. It is limited to numeric variables and needs to normalize variables.

Naïve Bayesian has quick calculations and it is easy to implement. This model is aapplicable for high-dimensional data and unrelated features and can be used with categorical variables.

SVM can control the overfitting. It is capable to model non-linear problems and can produce a high value of accuracy. However, it is memory intensive, inappropriate for large datasets and produces uninterpretable results.

The methods of constructing machine learning models are described in detail in the papers[16-20]. Besides, given the good results that deep learning methods have produced in recent years in various fields, deep learning model has been presented and the results have been evaluated and compared according to different evaluation criteria. The target variable in these models can be either "without complication" or "with complication" according to the existing data.

The following is a brief explanation of how learning models work.

Classic learning models

Simple Bayesian model

The simple Bayesian model is based on the Bayesian conditional probability rule and is appropriate when the number of independent inputs is large .

Logistic regression

It is derived from linear regression and is used when the response variable has 2 states of Y = 1 or Y = 0. This method uses a function to communicate between the explanatory variables and the response variable, and does not consider a linear relationship between them.

C5.0 decision tree

A decision tree has a root node that other nodes are leaves of that tree that are branching from the root of the tree. All the elements of the tree are connected to each other by roots. Each node implies a test on an attribute. In terms of the number of an attributes, the main node splits into several other nodes. The leaves at the end of the branches determine the final class of an example.

C5.0 decision tree is a newer version of the C4.5 decision tree that can create both binary and multipoint trees. In this tree, the entropy criterion is used for branching.

CART decision tree

By this algorithm classification and regression tree can be carried out. The tree uses the Gini index criterion for branching. This tree can have both numeric and nominal attributes.

Support vector machine

The support vector model performs the classification by constructing a multi-dimensional hyper plane which divides the data into two class. The purpose of this model is to find optimal algorithms that separate the data in such a way that the target variable is located on one side of the plane belongs to a class and those belonging to other classes on the other side of the plane.

Random forest

The random forest decision tree, or RF, consists of a large number of decision-makers which act as a group. Each tree in RF offers a prediction, and eventually the class that is more selected by the trees is returned as a result.

Deep learning

Deep learning is a neural network method that model high-level abstract concepts in data using some linear and nonlinear conversion layers, and returns the output[21]. This algorithm automatically selects the necessary and relevant features to solve the problems.

In deep learning, each hidden layer is responsible for training a set of unique features that operate on the basis of the previous layer's output. The complexity of the model rises by adding more extra hidden layers. Moreover, this type of hierarchical learning transforms low-level features into high-level features. Therefore, the deep learning method solves complex problems involving many nonlinear layers.

Method

In this study, we used Design Science Research (DSR) paradigm as the research methodology. DSR is fundamentally a problem-solving paradigm that seeks to enhance human knowledge with the creation of innovative artifacts. We conducted the DSR methodology proposed by Peffers et al[22]. This approach consists of six steps: problem identification, definition of the expected results, design and

development, demonstration, evaluation and communication.

Data

In the current study, adult thalassemia was studied. The cross-sectional data were collected from the records of 12 thalassemia centers in Tehran province and 14 thalassemia centers in Mazandaran province in 2018. The total number of records available was 3489, of which 138 reported post-injection complications.

According to the background of the study and consulting the specialists, the variables of this study are classified into groups including the history of patients' health, demographic data, body examination, laboratory data, blood injection information, biochemical data, immunologic, hematologic, medicinal and vaccination information. Finally, the relevant variables that were common and accessible in most centers, along with the descriptive analysis of the variables, are presented in Table 2.

Table 1- List of variables used to predict blood injection complications.

Type of	Name of variable	Statistical analysis
Demographic	Age	Between 15 to 72 with an average of 38.06
	Gender	52.2% of patients were male (1821) and
	Kinship status of parent	41% of parents were relatives
	Age of diagnosis	From 2 months to 50 years
	Age of first blood transfusion	From 2 months to 50 years
History of health	History of the reaction during	60% history of reaction during blood
	History of splenectomy	48% has the history of splenectomy
	Bone marrow transplant history	1.7% has the history of bone marrow
	HIV	2.9% HIV patients
	Hepatitis	23% Hepatitis patients
Medicinal information	Desferal consumption	78% consumed desferal
	The age of onset of desferal	From 3 months to 62 years
	Taking other iron detergent	60 % consumed other iron detergent
Blood injection information	Type of thalassemia	68 % major thalassemia (2373), 29%
	Blood type	O+ 33.6%, O- 5.5%, A+ 29.5%, A- 2.3%,
	Blood injection frequency	From 15 to 180 days with average of 29.8
	Blood Filter Status	9.9% use of filter
Vaccination	Hepatitis vaccination	90.7 % received hepatitis vaccination

In this study, due to the low incidence of post-transfusion complications, we considered all records that had any type of complication after blood transfusion (except complications caused by human errors) as "complication" class (138 records) and records with no complications were considered as "normal" class (3351 records).

The data under study had various challenges that neglecting them could bias the results, including missing values, outliers, and severe imbalance of data classes.

Preprocessing

To fix the missing values problem, we removed from the normal class all records containing missing values (1027 records deleted and 2324 records remained).

However, due to the low number of complication samples, we did not eliminate such records from the complication class, but completed the missing values with the MICE method[23]. For prognostic factors studies in medicine, multiple imputation is becoming the standard route to estimating models with missing data under a missing-at-random assumption[24]. The MICE technique, using other columns values, completes an incomplete column. Each incomplete column is considered as a target variable. The default setting of the predictive variables is all columns other than the target variable.

In order to overcome the problem of outliers, the appropriate domain was determined for the variable with respect to the opinion of medical experts. The values outside the range were removed and then calculated and completed using the MICE method.

Another problem with the research data was the uneven distribution of data classes. After deleting missing values, only 5.6% of the records belonged to the complication class. Traditional classification methods do not perform well with unbalanced data because these algorithms evaluate the overall performance of the data and classify all data into the majority class. There are many ways to deal with unbalanced data that are generally grouped into two categories of "data-level "and "algorithm-level ". Both approaches have been examined. At the algorithm level, the cost function method was used. At the data level, NearMiss used for under sampling and SMOTE for over sampling. Ultimately SMOTE produced better results. In this method, using the nearest-neighbor algorithm, synthetic but similar observations of the minority class are produced, while the majority class observations are also reduced. This operation balances the number of minority and majority class observations and often improves prediction results[25] .

In order to produce more reliable results, all features were scaled using MinMaxScaler method. In this approach, the data is scaled to a fixed range (usually 0 to 1).

Feature Selection

According to the prediction methods used in this study, the methods of data analysis are divided into two categories: classical algorithms and deep learning method. In preparing data for classical methods, 12 best variables were selected using SelectKBest method. SelectKBest is basically just a wrapper that keeps a set amount of features that are the highest ranked according to some criterion. In this case, we used the p-values of completed hypothesis testing as a ranking.

The list of selected variables and their ranges are shown in Table 3.

Table 2- Variables of classical methods.

	Name of variable	Domain of variable
1	Age	Teen, young, middle-aged, old
2	Gender	Male, Female
3	Parents kinship	Has, Doesn't have
4	History of the reaction during	Has, Doesn't have
5	History of splenectomy	Has, Doesn't have
6	Bone marrow transplant history	Has, Doesn't have
7	HIV	Has, Doesn't have
8	Hepatitis	Has, Doesn't have
9	Desferal consumption	Has, Doesn't have
10	Taking other iron detergent	Has, Doesn't have
11	Type of thalassemia	Major, intermediate, alpha, sickle
12	Hepatitis vaccination	Has, Doesn't have

For preparing the data for the deep learning method, all variables were considered. We used one-hot encoding to convert nominal variables into numerical variables. It caused the number of input variables to be increased.

Modeling and results

In this section, we first describe the criteria for evaluating models, and then we model and evaluate the results.

Evaluation criteria

The three most important evaluation criteria in this study are the sensitivity, precision,

and f1-score criteria, which are calculated as follows:

$$Precision = {TP}/{(TP + FP)}$$

$$Sensitivity = {TP}/{(TP + FN)}$$

$$F1 - measure = 2.\frac{(Precision.Sensitivity)}{(Precision + Sensitivity)}$$

Which TP is true positive, FP is false positive, and FN is false negative.

Since we intend to identify all those at risk as far as possible, the sensitivity values should be maximized. Besides, the number of false alarms should be reduced as much as possible, so precision should be high to avoid overburdening and operating costs to health systems. In this paper, we apply the F1-measure criterion as the primary criterion for model comparison, which is the harmonic average of sensitivity and precision. Moreover, in order to implement a warning system in the real world, a high degree of specificity is required. Therefore, it is necessary to balance the sensitivity and specificity criteria. ROC curve graphically displays the trade-off between sensitivity and specificity. The area under ROC curve (AUC) provides a useful parameter for evaluating the performance. FPR indicates the number of false alarms and it is desirable to have a low value.

It should be noted that in highly unbalanced sets, high accuracy cannot be a measure of model superiority, because if a model incorrectly classifies all minority class samples as the majority class, the accuracy value will still be high. On the other hand, since the number of positive samples is much less than the number of negative samples, even a small amount of FPR generates a large number of false alarms (FP) and reduces the amount of precision. As a result, it is very difficult to have an acceptable precision with a high value of sensitivity with imbalanced datasets. But the AUC criterion, which indicates the power of the model to distinguish between two classes, does not have a dependence on the equilibrium status of the data classes.

Modeling

At first, a number of classical models and then deep learning methods were trained. We aimed to find out which learning algorithm produces better results. In addition, we used the output of classical models as input features for deep learning method to find out whether it improves the results or not.

All machine learning activities were carried out in python3 language in IPython environment. Models were validated by k-fold cross validation. In this method, the data are randomly classified into k subsets. Training and test are performed k times once a set is kept for model testing and others are used to train the model. It is repeated k times as each of the subsets is used once to test the model. Finally, the result of this k iteration is averaged to obtain a final estimate. Stratified 10-fold cross-validation was used to evaluate the models. In this method, subsets were classified in such a way that there was a similar ratio between the groups.

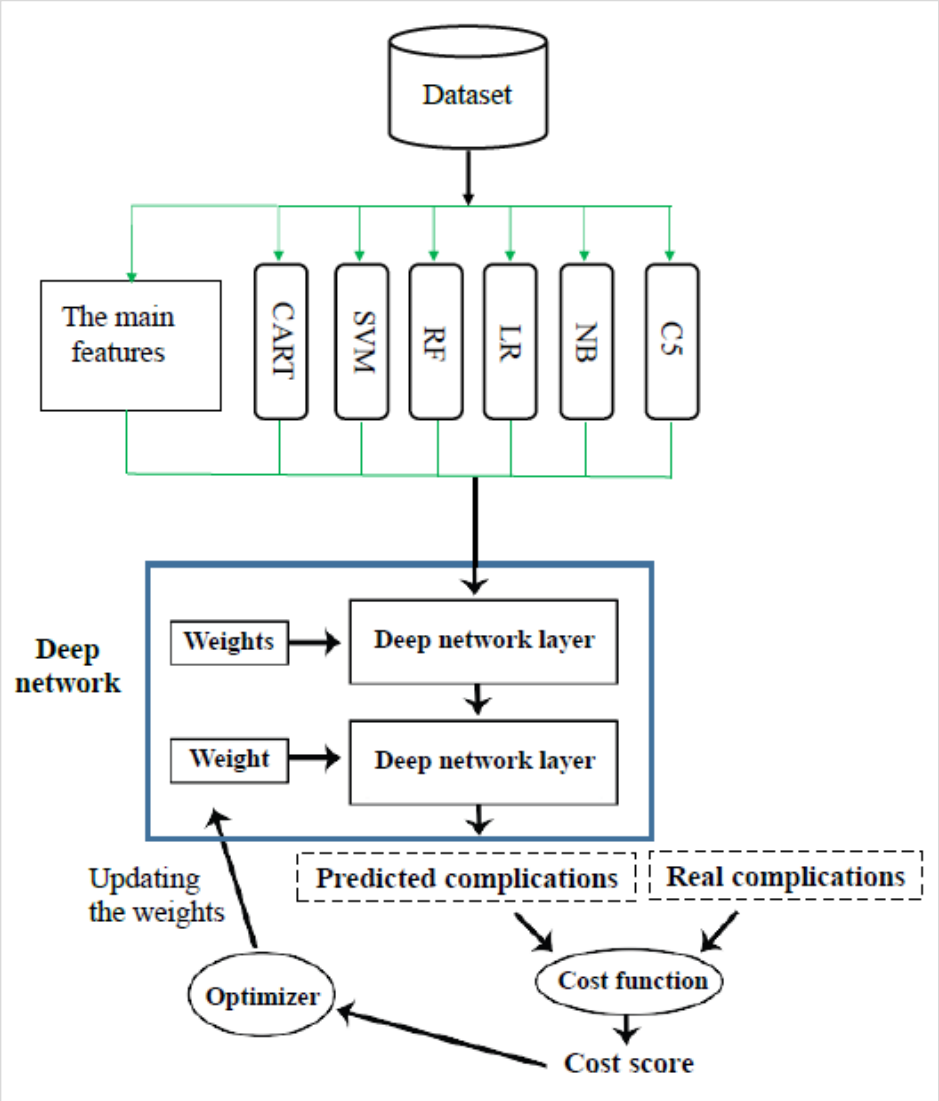
To train the models, the data set was first cross-validated into two training and test sets, then each pre-processing step was performed separately for the two training and test sets. It worth noting that balancing is performed only for the training data set. The learning model was trained on the train data set and tested on the test data set. In addition, for each machine learning model, the best-performing hyper parameters were selected using the Grid

search method. The best performance was determined by the f1-score criterion. Finally, the mean of different iterations was recorded for each model.

In the next step, the deep learning method was examined. In order to prepare the data for deep learning model, each single data point was encoded as a vector, and thus a batch of data was encoded as a 2D tensor (that is, an array of vectors), where the first axis is the samples axis and the second axis is the features axis.

At first, deep learning model was used with base features. Then, in order to improve the prediction results, we used the deep learning technique with a combination of classic models. The prediction output of the classic models for each record of data (which is 0 or 1) was considered as a set of new features and added to the set of original features. As mentioned earlier, the deep learning model learns features directly from data without the need to select attributes. In Figure 1 you can see the main components of the proposed deep learning model.

Figure 1- The proposed deep learning model for predicting post-injection complication



In this paper, the Keras sequential model was used to implement the Deep Dumb MLP (DDMLP) learning model. Since the addition of more than 5 layers had no effect on the results, we used 5 layers to minimize the learning parameters. The first layer received 49 features as input variables including the features produced through one-hot encoding (39 features), the numerical variables (4 features) and the output of classic models (6 features). In this study, simple vector data, stored in 2D tensors of shape, was processed by densely connected layers, (the Dense class in Keras).

The three key elements of the model are *Last-layer activation function*, *Loss function* and *Optimization configuration* (26). Since our problem was a binary classification, we used Sigmoid activation function for the output layer. The sigmoid activator output is a probability (between 0 and 1) indicating how likely the target variable is to be positive. We examined various activation functions for hidden layers that ReLU[1] produced the best results. The binary cross-entropy function was chosen as the cost function.

To optimize the model Adam optimizer was used with the default parameters. We used dropout method to regularize the model. The number of replicates was selected between 20 and 80 and the values of 32, 64 and 128 were examined as mini-batches.

Results and comparisons

Table 4 presents the best results for classical and deep learning algorithms to predict the post-transfusion complication.

[1] Rectified linear unit

Table 3- Best results for predicting post-transfusion complications with classical learning algorithms.

Method	Accuracy	Precision	Sensitivity	F1-score	AUC	FPR	Specificity
C5.0 Decision tree	0.75	0.04	0.61	0.08	0.71	0.24	0.76
CART Decision tree	0.88	0.06	0.43	0.11	0.76	0.12	0.88
Random forest	0.86	0.06	0.77	0.11	0.60	0.24	0.76
Logistic regression	0.69	0.14	0.72	0.24	0.74	0.31	0.69
Naïve Bayes	0.88	0.06	0.43	0.11	0.76	0.12	0.88
SVM	0.71	0.16	0.71	0.25	0.77	0.29	0.71
Deep learning	0.76	0.21	0.77	0.33	0.74	0.24	0.76

As stated earlier, since we aimed to identify the highest number of complications and to reduce false alarms, we considered the f1-score criterion for comparing models. It is the harmonic average of the two criteria of sensitivity and precision. Based on this criterion, deep learning models produced higher values for f1-score. In addition, the use of the proposed hybrid dataset to train the deep learning model improves the sensitivity and precision values and thus the f1-score.

If our goal was to maximize other performance measures, other algorithms would be chosen as optimal. For example, CART Decision Tree and Naïve Bayes algorithms produce the highest accuracy, or the deep learning model with the basic dataset yields the highest AUC.

We also attempted to compare the proposed prognostic model with similar work carried out in previous studies. The comparison results are presented in Table 5.

Table 4- Comparing the proposed model with related studies.

Reference	Population	Method	Accuracy	Precision	Sensitivity	F1-score	AUC	FPR	Specificity
(18)	3398 patients, 143 TACO &	Sparse LDA	0.73		0.89		0.84		0.72
(19)	3398 patients, 143 TACO &	Tree bag	0.71		0.82		0.83		0.71
(20)	40 control, 21 TRALI	CART			0.73				0.57
	40 controls, 20 TACO				0.9				0.56
The proposed model			0.76	0.21	0.77	0.33	0.74	0.24	0.76

These articles differed in several aspects, such as the variables used and the extent of the balance of data classes with the current research. Moreover, the three most important criteria in the current study were precision, sensitivity, and f1-score, and were intended to maximize the f1-score,

but other researchers have taken into account the maximization of other criteria. They have not provided values for the three most important criteria in the current study simultaneously. Therefore, due to the lack of sufficient information, it is not possible to obtain an accurate estimate of the improvement the proposed model produced compared to similar works.

Conclusion

In this paper, using artificial intelligence algorithms, we predicted the risk of blood transfusion complications in thalassemia patients. Classical models and deep learning methods were investigated. We selected f1-score criterion for the assessment of the models, which is the harmonic mean of sensitivity and precision. This way, in addition to the diagnosis of a high percentage of patients at risk of the complications, the number of false alarms was also reduced. Finally, the deep learning method produced better results for predicting the risk of a complication (f1 - score = 0.33, sensitivity =0.77, precision = 0.21).

The main contributions of this paper are: prediction of transfusion complications using deep learning method and proposing a hybrid dataset to improve the results.

The limitation of the current research is that the optimal model is developed using deep learning methods that are black box techniques. In such techniques, the reasons for model decisions are unclear and the results cannot be interpreted. In future studies, it is desirable to derive a set of intuitive and comprehensible rules. Moreover, despite the improvements, the value of precision is low. In order to improve the results, the model needs to be updated with more data. In addition, the proposed prognostic model can be developed to be used for other patient groups.

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