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Automated detection of diabetic retinopathy using machine learning classifiers

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Abstract. – OBJECTIVE: Diabetic Retinopathy (DR) is a highly threatening microvascular complication of diabetes mellitus. Diabetic patients must be screened annually for DR; however, it is practically not viable due to the high volume of patients, lack of resources, economic burden, and cost of the screening procedure. The use of machine learning (ML) classifiers in medical science is an emerging frontier and can help in assisted diagnosis. The few available proposed models perform best when used in similar population cohorts and their external validation has been questioned. Therefore, the purpose of our research is to classify the DR using different ML methods on Saudi diabetic data, propose the best method based on accuracy and identify the most discriminative interpretable features using the socio-demographic and clinical information.

PATIENTS AND METHODS: This cross-sectional study was conducted among 327 diabetic patients in Almajmaah, Saudi Arabia. Socio-demographic and clinical data were collected using a systematic random sampling technique. For DR classification, ML algorithm including, linear discriminant analysis, support vector machine, K nearest neighbor, random forest and its variate ranger random forest classifiers were used through cross-validation resampling procedure.

RESULTS: In classifying DR, ranger random forest outperforms the other methods by accurately classifying 86% of the DR patients on the test data. HbA1c ($p<0.001$) and duration of diabetes ($p<0.001$) were the most influential risk factor that best discriminated the DR patients. Other influential risk factors were the body mass index ($p<0.001$), age-onset ($p<0.001$), age ($p<0.001$), systolic blood pressure ($p<0.05$), and the use of medication ($p<0.05$) that significantly discriminated the DR patients.

CONCLUSIONS: Based on the present study findings, integrating ophthalmology and ML can transform diagnosing the disease pattern that can help generate a compelling clinical effect. ML can be used as an added tool for clinical decision-making and must not be the sole substitute for a clinician. We will work to examine the classification performance of multi-class data using more sophisticated ML methods.

Key Words:
Machine learning, Ranger random forest, Diabetic retinopathy.

Introduction

Diabetes Mellitus (DM) is one of the most prevalent chronic debilitating diseases worldwide. About 63 million people, 1 in 11 are affected by DM, and 1 in 2 people are undiagnosed[1]. The most threatening microvascular complication of DM is Diabetic Retinopathy (DR). Early detection of DR is essential for treatment success. However, at the early stage, this disease has no specific symptoms, therefore making it really challenging to diagnose[2,3]. The diabetic patients must be screened annually for DR. However, it is practically not viable to achieve this goal due to the large volume of diabetics, lack of resources, economic burden, and cost of screening procedures. In-addition, even clinicians sometimes could

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not timely diagnose the DR[4-6]. The World Health Organization (WHO) report published in 2018 stated that there are more than 4.5 million diabetics in the Kingdom of Saudi Arabia (KSA), thus making its prevalence as one of the highest in the world[7]. The Kingdom capitalized around 1,142 M$ for surmounting this disease, which is enormously influencing its workforce. According to one report of W.H.O, KSA is spending almost 800$ on an individual diabetic, making the annual cost soaring up to $9.6 billion for its diabetic population[8]. The prevalence of DR is also increasing at an alarming rate in KSA; in 2002, it was 1.3% that increased to 30% in 2010; in 2016, the prevalence sored up to 35.8%, and in 2019, it reached 44.7%[9-12].

The use of Machine Learning (ML) in medical science is an emerging frontier, the tasks can be accomplished by the minimal involvement of humans and somehow with more accuracy. In ophthalmology, the use of Artificial Intelligence (AI)/ML can focus on diagnosing DR, Glaucoma, Age-related Macular Degeneration (ARMD), Retinal Vein Occlusion (RVO), Cataract and Retinopathy of Prematurity (ROP)[13,14]. There are many clinical benefits of using ML algorithms in detecting irreversible visual impairment diseases like glaucoma, DR and ARMD. Integrating ophthalmology and ML has the capability to transform diagnosing the disease pattern that can help in generating a compelling clinical effect[15]. A study conducted in Spain[16] used three different classification ML algorithms for detecting the DR; Random Forest (RF) performed the best with an accuracy of 80%. The Food and Drug Administration (FDA), USA also developed an AI-algorithm for the detection of DR, with Support Vector Machine (SVM), results showed an accuracy of 82%[17]. There are few available ML algorithms for the detection of DR, but their performance has been criticized in the literature[18]. This leads to develop a strong interest in proposing a ML model that can help in detecting DR in Saudi diabetic patients by inspecting the socio-demographic and clinical data. This is the first study in KSA that have used the ML algorithms in predicting the DR; we have applied various supervised ML algorithms like Linear Discriminant Analysis (LDA), SVM, K-Nearest Neighbor (KNN), RF, and Ranger Random Forest (RRF) on the DR data. The accuracy of each of the methods was evaluated and is presented in the subsequent sections.

Patients and Methods

This cross-sectional study was conducted among diabetic patients in Almajmaah city located in KSA from September 2019 - February 2020. The diabetic patients are registered at eight Primary Healthcare Centres (PHCs) in Almajmaah city and referred to one main secondary care King Khaled General Hospital. The target population was composed of all Saudi diabetic males and females registered in all PHCs. Level of precision formula was used to calculate the sample size based on the previous prevalence of DR=30.7% (z=1.96, p=0.307, 1-p=0.693, d=0.05)[19,10]. The minimum required sample size calculated by the formula was 320. In the data collection and its cleaning phase, several errors (outliers, patients withdrawing from the study, sampling, and typographical errors, etc.) might occur that can affect the sample size. To maintain the minimum required sample size number corresponding to the power of study, the data was collected from 327 patients using a systematic random sampling technique with proportional allocation. This research was approved by the Basic and Health Sciences Research Centre (BHSRC) vide approval no MRIE07/BHSRC1084/2019. The division of the questionnaire was done in two parts; the initial part consists of socio-demographic data (age, gender, BMI), risk factors (hypertension, myopia, heart disease, kidney disease, and hypercholesteremia), and clinical data (age-onset, duration of diabetes (DoD), HbA1c (marker for diabetes control), Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), and medications). Overall, 14 predicting features were used in this study. The second part consisted of a complete Ophthalmic Examination (OE). The OE was done by a consultant ophthalmologist. The OE comprised (Visual Acuity (VA) measurement for distance, which was taken using Snellen distance visual acuity chart at 6 meters; anterior segment examination using Haag Streit slit lamp model and dilated fundus examination with slit lamp +90-diopter volk lens and indirect ophthalmoscopy).

Multivariate Outlier Removal for the Diabetic Retinopathy Data

For better classification and skillful predictions through supervised ML classifiers, outliers are required to be identified and removed from the data before proceeding with the modelling analysis. A multivariate outlier removal method has opted for the DR data where each variable was examined for the presence or absence of outliers; the results were then modelled onto all other variables using an RF imputation procedure. In this procedure, the computed scores reflect the absolute differences between the observed value and out-of-bag prediction using a pre-determined threshold criterion. The outlier removal process is presented in Figure 1. Results showed that only three observations had an absolute difference between the observed value and out-of-bag prediction above the threshold value of 4; therefore, they were considered outliers. These observations belonged to DoD, BP Diastolic, and BMI. By discarding the respective three patients' information from the sample, the final data set contained 324 samples, which was higher than the original estimated sample size of 320.

Linear Discriminant Analysis (LDA)

LDA comes under the auspices of supervised ML classifiers, which assumes that the predictor factors (X) are homogenous for each DR class and follow a multivariate normal distribution[20,21]. In LDA, the decision boundary for the classes is determined by , here is the variance-covariance matrix of the predictor factors, i.e., the socio-demographic and risk factors, is the mean vector for DR class , and are the prior probabilities that are of the size proportional to the respective class .

K-Nearest Neighbors (KNN)

KNN is another potential candidate for a supervised ML classifier, which utilizes the dissimilarity method for the classification of a new observation. The dissimilarity is usually computed by Euclidean distance. In KNN classification, the output is a class membership. An object is classified by its neighbors' plurality vote, with the object being assigned to the class most common among its K nearest neighbors[22-24]. KNN algorithm depends on K; larger values of K reduce the effect of noise on the classification but make the boundaries between classes less distinct. It is usually tuned by cross-validation resampling procedure.

Support Vector Machine (SVM)

SVM is another supervised ML algorithm that is used for classification purposes. We used the SVM algorithm in this study to predict the presence or absence of DR. The algorithm works by building a hyperplane in a high dimensional space. A hyperplane is a set of points of data matrix which satisfies where is the normal vector to the hyperplane. The parameter determines the offset of the hyperplane from its origin along the normal vector[25,26].

Random Forest (RF) and Ranger Random Forest (RRF)

RF is another prominent ML method; it is an ensemble tree-based learning algorithm[27]. The RF classifier is a set of decision trees that are made from the randomly selected subset of training patients data. It aggregates the votes from different decision trees to decide the final class of the test object, majority votes of all predicted classes over B trees. As the RF computations are

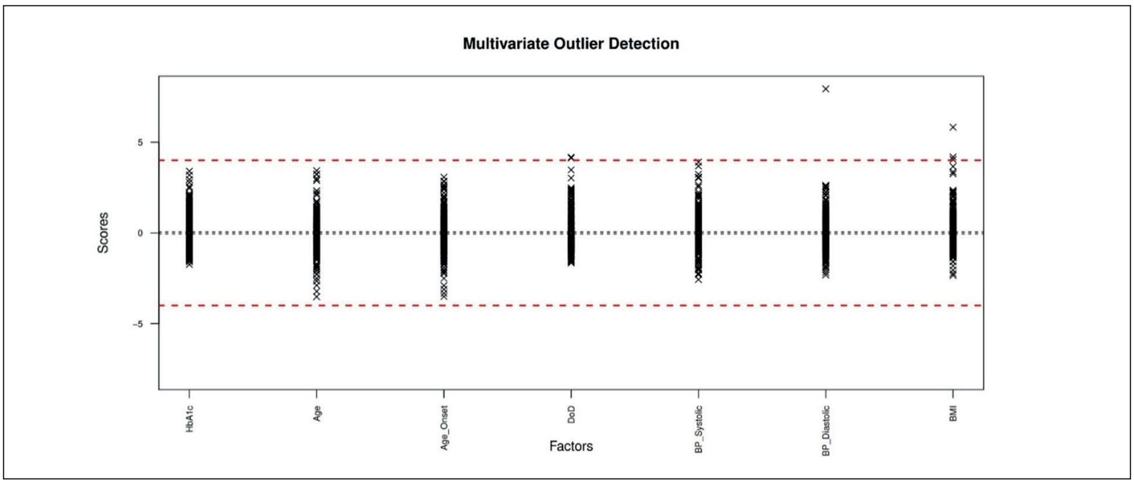

Figure 1. Multivariate outlier removal – where each quantitative variable is examined for outliers is modelled onto all other variables using a RF.

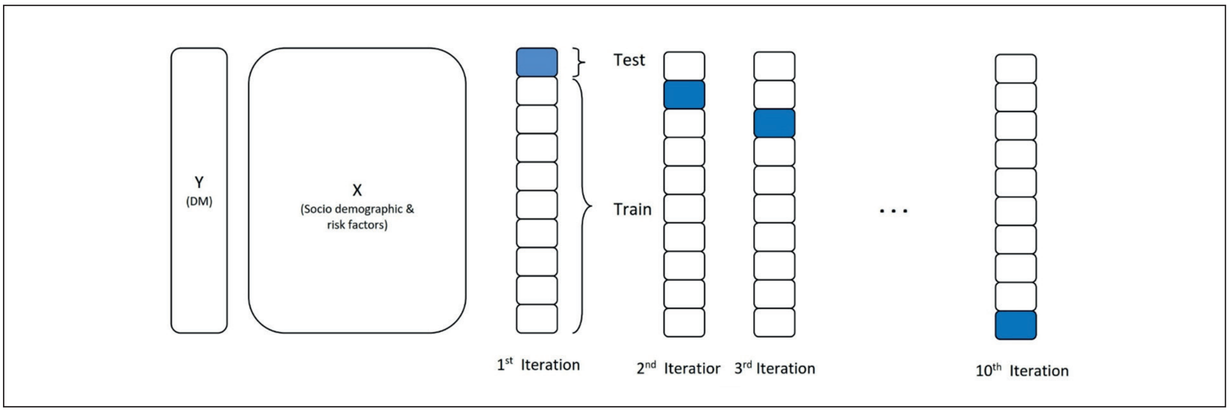

Figure 2. One run of 10-fold cross-validation.

complex, there are several variants of RF such as RRF[28,29] that can help facilitate these complex computations. The RRF algorithm provides a fast and efficient calculation by using the recursive partitioning framework.

Validation of Diabetic Retinopathy Classifiers

To obtain valid and reliable results, the DR classifiers must be validated; this means how good these classifiers are in predicting a new patient with the presence or absence of DR; this is usually observed by calculating the validated accuracy. Its accuracy ranges from 0 to 100%, a high % age indicates that the respective DR classifier is preferable over the others. For testing the validation, several schemes exist. In this research, we have used a 10-fold cross-validation resampling technique that was repeated 100 times. One run of 10-fold cross-validation is presented in Figure 2. The 10-fold cross-validation contains 10 iterations, and in each iteration, the DR response and data matrix is divided into 10 folds. In the 1st iteration, except the 1st fold, the remaining nine folds are used to train the DR classifiers. The accuracy of the trained classifier is measured on test data. In the 2nd, iteration the validated accuracy of the classifier is measured from 2nd fold, and so on. At the end, the accuracy of the respective classifier from each iteration is averaged for that specific run.

Results

The information of 324 patients was used to classify DR's presence and absence by applying 10-fold cross-validation. A sample of 100 was used to train the DR classifiers (LDA, KNN, SVM, RF, and RRF). The comparison of the validated accuracy of these classifiers is presented in Figure 3. It was observed that the KNN classified 74% of the patients truly as having DR or not on the test data. The validated accuracy of LDA and SVM was similar to around 80%, respectively. SVM showed less variation in the validated accuracy as compared to LDA. RF in its standard from classified 82% of the patients truly as having DR or not on the test data, while its advanced variant RRF classified 86% of the patients truly as having DR or not on the test data. This indicated that RRF best classified the DR patients as compared to the other ML classifiers.

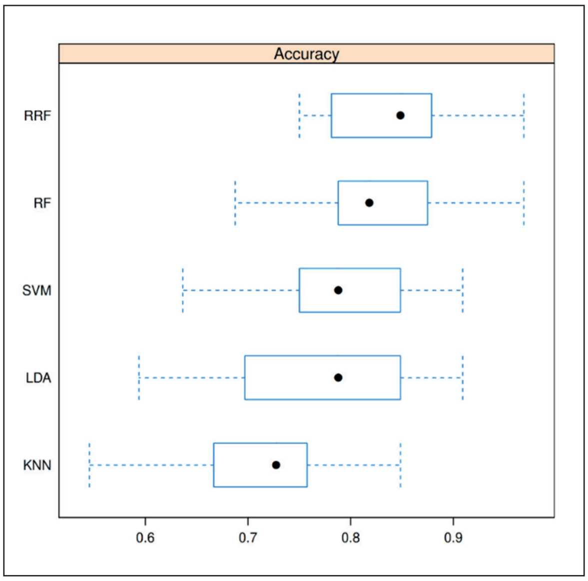

Figure 3. The comparison of validated accuracy of DR classifiers – LDA, KNN, SVM, RF, and RRF.

By using the best fitted RRF model, the socio-demographic and clinical risk factors along their mean decrease in Gini are presented in Figure 4. A risk factor having a mean decrease in Gini of at least 10 was considered as influential. It appeared that HbA1c was the most influential risk factor (p<0.001) that discriminated the DR patients. Next to HbA1c were the risk factors DoD (p<0.001), BMI (p<0.001), age-onset (p<0.001), age (p<0.001), BP Systolic (p<0.05), and the use of medication (p<0.05) that significantly discriminated the DR patients. One of the tree from RF, which classified the DR patients by using the above mentioned influential risk factors, is presented in Figure 5. This reconfirms that HbA1c is the most important factor which discriminated the DR patients. This specific tree provides the threshold on risk factors with their several conditional structures. For instance, if a patient has HbA1c less than 6.9 then he/she is not likely to be a DR patient, but if a patient has HbA1c greater than or equal to 6.9 and is on insulin than he is likely to have DR. Similarly a person having HbA1c greater than 9.4, DoD is less than 9 years, and age-onset is less than 33.5 then the patient is more likely to be classified as having DR.

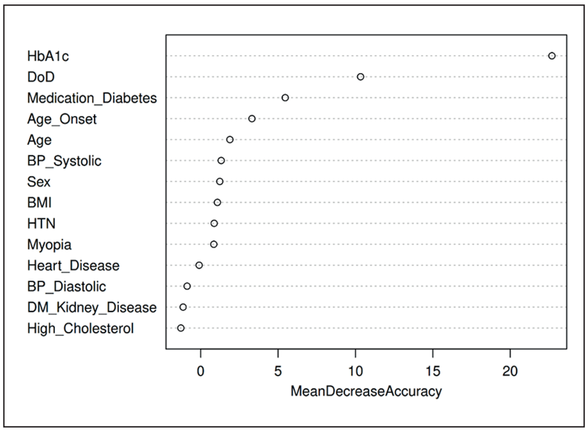

Figure 4. The risk factors extracted by RRF are presented along with their mean decrease in Gini.

Discussion

This is the first study in KSA that has proposed an accurate and clinically interpretable model for classifying the DR. We applied SVM, LDA, KNN, RF, and RRF to predict DR with 10-fold-cross-validation. RRF outperformed other ML methods by achieving an accuracy of 86%. HbA1c was the most influential risk factor in discriminating DR patients followed by DoD, BMI, age, age-onset, SBP, and use of medication. Tsao et al[30] compared various ML algorithms with 5-fold cross-validation to classify DR; results showed that SVM outperformed the other ML methods with an accuracy of 79.5%; moreover, medication and DoD were the most significant predictors of DR. In comparison, our study used 10-fold cross-validation and results reported a

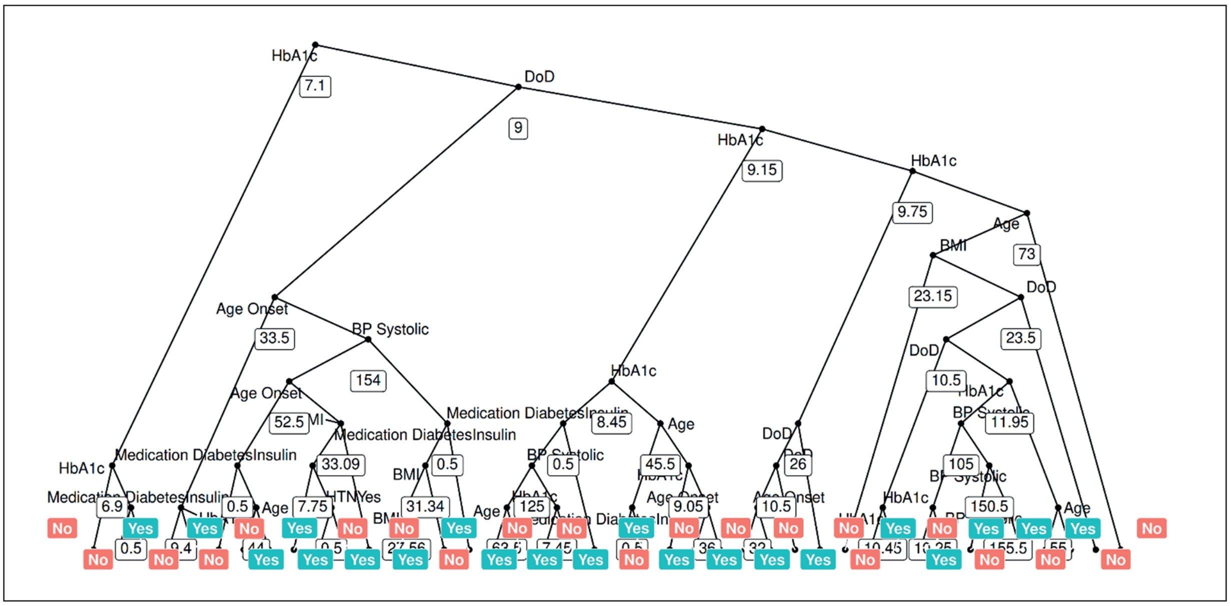

Figure 5. One of the trees from the random forest which classifies the diabetic retinopathy patients.

higher accuracy in predicting DR, in-addition, apart from the use of medication and DoD our study reported additional significant clinical features in predicting DR. Our results again reported a higher accuracy of 86% in predicting the DR than what was reported by a study conducted in Spain[16] in 2016 that stated the accuracy of 80% using RF. In this case, the variate RRF clearly performed better than the classical RF algorithm.

Ramya[18] in 2018 used SVM to predict DR; results reported an accuracy of 82%; comparing these results with our study showed that RRF clearly has a better performance in predicting DR as compared to SVM. Another study conducted in 2018 by Maliha et al[31] applied SVM, KNN, RF, and Neural Network (NN) to classify DR; of note, NN was the best DR classifier with an accuracy of 75.32%, whereas the classification accuracy of RF was 63.63%; both these classifiers underperformed RRF that in our study had an accuracy of 86%. A study conducted in South Korea by Oh et al[32] used least-absolute shrinkage and selection-operator in combination with Bayesian Information Criteria to predict DR from a sample of 490 randomly selected patients; their results reported an accuracy of 73.6%, clearly in comparison to our study RRF outperforms the usage of sparse-learning models by predicting DR with an accuracy of 86%. This evidently highlights the importance of conducting research in similar population cohorts, and it places a question mark on the external validation of the various ML algorithms.

A study conducted in the United States by Ogunyemi et al[33] used ensemble classifiers to predict DR from the data of 513 patients; the reported accuracy was 73.5%. Again, our study results reported a higher predicting accuracy of 86% as compared to 73.5%. Casanova et al[34] in 2014 predicted DR using RF with two-fold cross-validation; results showed an accuracy of 75% with medication and DoD as the most influential variables. In comparison, firstly, when we applied the RF in standard form, our results reported a higher accuracy of 82% using 10-fold cross-validation; secondly, when the variate RRF was applied, the accuracy increased to 86%; thirdly, apart from medication and DoD out study showed the importance of examining HbA1c, BMI, age, age-onset and systolic BP that can help in predicting early DR. Rajkumar et al[35] used two ML algorithms, i.e., gradient descent and SVM to classify DR, the reported accuracy was 84% and 63% respectively. In contrast, SVM in our investigation reported a higher accuracy value of 80%, and additionally, by using RRF, the accuracy soared-up to 86%. This shows that SVM, which is being applied classically to predict DR, has underperformed than RF and its variate RRF, as asserted in our study. Kader et al[36] applied non-linear SVM kernels with hyperparameter optimization to improve the performance of classifying DR; the results indicated an accuracy of 85.45%, which is again less than what has been stated in our study.

Although the RRF showed good results in classifying DR, nevertheless all ML methods should be applied with caution, sometimes due to their nature, it might become difficult from interpretation point-of-view that how these algorithms make the decision. As this is the era of "evidence-based medicine", ML algorithms' results must be used as a guided approach in consultation with the clinicians. Though using them can help in the larger screening of the population at risk of developing the disease. Above all, to improve the applicability of AI/ML in clinical setting needs building an interpretable systematic AI/ML platform(s) using appropriate multimodal data embedded with advanced techniques. Despite some ethical and regulatory issues, AI can still make a remarkable contribution in revolutionizing the present diagnostic pattern of disease and creating a significant clinical effect in the near future.

The use of insulin and DoD are well-established risk factors for developing DR; however, in our study, we have found other important discriminative clinical features that can clearly differentiate between DR and non-DR. Traditionally most of the published studies have used SVM in classifying DR, whereas we have applied various ML algorithms to find the best predictor for our population; the RRF outperformed the others in terms of accuracy. Moreover, to bring the proposed ML method into effect, for initial screening, we can create a website or an android application where the prediction of DR for new patients can be made; this will surely help in reducing the volume of patients referred to the ophthalmologists, and the cost involved in screening the patients can be minimized.

Apart from a number of strengths, there are certain areas where improvements can be made. The analysis was based on ophthalmologist-graded funds photography data. We assume that this classification, if performed automatically through pattern recognition algorithms by quantifying the subtle patterns in the images data, can help in making even more accurate predictions. Although supervised ML algorithms can classify multiple NPDR categories (mild, moderate, severe), the classification accuracy drops when working with multi-categorical data. Moreover, the influential factors that have explained the variation in the NPDR category can be interpreted in a better way when working with binary response. The ML-based prediction can assist clinicians to improve the diagnostic efficiency, reliability, and accuracy. It can also assist them to evaluate the patients' risk scores timely, quickly and efficiently, i.e., upon patient's admission. This aided benefit can help the clinicians in planning and providing tailored care to the patients with low cost of care and increased patient satisfaction, ultimately leading to better outcomes.

Conclusions

We applied various ML classifiers in predicting DR. RRF outperformed the other classifiers by achieving an accuracy of 86%. The algorithm also identified HbA1c and duration of diabetes as the most discriminating interpretable features for classifying DR; other significant socio-demographic and clinical features include BMI, age-onset, age, SBP and use of insulin. Based on our results, a clinical decision support system can be built for future clinical practice. AI/ML should always be used as an added tool for clinical decision-making and must not be the sole substitute for a clinician. We will examine the classification performance of multi-class data using more sophisticated ML methods and more advanced data.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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