Journal of Advanced Research in Applied Sciences and Engineering Technology 59, Issue 5 (2026) 262-274

SEMARAK ILMU PUBLISHING

Journal of Advanced Research in Applied Sciences and Engineering Technology

Journal homepage: https://semarakilmu.com.my/journals/index.php/applied_sciences_eng_tech/index
ISSN: 2462-1943

Unlock the Recent Prediction Models using Clinical Variables for Diabetic Retinopathy

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ARTICLE INFO

Article history:
Received 27 November 2026
Received in revised form 20 February 2026
Accepted 15 April 2026
Available online 4 May 2026

Keywords:
Prediction models; Artificial intelligence; Diabetic retinopathy; Retinal Screening; Type 1 and type 2 diabetes

ABSTRACT

Diabetic retinopathy (DR) poses a major challenge to clinician and public health personnel due to the potential complication of vision loss especially among young adults. Thus, many studies came out with artificial intelligence prediction models for diabetic retinopathy to enhance the management of potential complication. The aims of this systematic review are to identify published prediction models using clinical variables for diabetic retinopathy and to compare their accuracy and quality. A systematic search was conducted in PubMed, Scopus, ScienceDirect, ProQuest, Web of Science databases. Studies were included if the model was applicable in type I or type II diabetes mellitus and the outcome was diabetic retinopathy. The methods of Checklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies (CHARMS) and Prediction model risk Of Bias Assessment Tool (PROBAST) were used as a guide. Ten studies since 2019 were identified and included here. Results of each model were compared in terms of area under ROC curve (AUC), sensitivity, specificity and others. This review provides an insight about the existing DR prediction models and to foresee the future prospects. Future work includes combination of prediction models using clinical variables with fundus images of the patients to predict the area possible for development of diabetic retinopathy.

1. Introduction

Diabetic retinopathy (DR) refers to damages to retinal vasculature and structural changes due to high blood sugar. By 2045, it is estimated that approximately 160.5 million of those of 700 million of people with diabetes will have DR [1] which is known to be the leading cause of blindness among working adults [2]. Thus, vigorous screening programmes have been carried out to detect DR at early stages to prevent blindness. It is good to have DR prediction models based on clinical variables or

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https://doi.org/10.37934/araset.59.5.262274

characteristics for social and economic reasons in the healthcare system. Diabetic patients can use the prediction model to time their ophthalmology clinic visit interval without much hassle.

Artificial Intelligence (AI) and machine learning (ML) have revolutionized many industries including medical field[3]. Ophthalmology is one of the medical areas that AI can help in detection, diagnosis, and prediction of ocular diseases such as diabetic retinopathy (DR)[4]. The ML algorithms have made data prediction models easier and simpler as compared to rigorous mathematical calculation that is involved in previous studies. A mathematical algorithm has been developed to calculate the risk of sight-threatening retinopathy (STR) based on epidemiological data and risk factors [5]. Besides, fuzzy rule-based system has been integrated as ML method for prediction of risk of developing DR [6].

Despite the growing importance of the screening tools for DR including direct and indirect ophthalmoscopy, slit-lamp exam, digital fundus photography, fundus fluorescein angiography, and automated DR detection software [7], there is room for DR prediction models based on clinical variables and characteristics. This is due to the fact that the prediction model for DR serves as a tool to alert the high-risk group for early treatment to prevent blindness. On the other hand, it also helps to reduce the cost for screening visits and to save on healthcare resources[8]. Many studies have explored various machine learning algorithms for prediction of DR progression. These models have intricate risk calculation from patients' clinical profile for determining the chances of developing DR and its progression and thus suggesting the screening intervals. It has been proven that the integration of machine learning technique in medical field provides promising predictive results.

The objective of this paper is to identify published works on prediction models using clinical variables for diabetic retinopathy applicable to type I and type II diabetes mellitus. Then, the machine learning models and modelling method were identified. In addition, the input predictors of each model were categorized and discussed. Subsequently, the selected prediction models were compared in terms of area under ROC curve (AUC), sensitivity, specificity and others.

The main sections of this paper include methods, result and discussion.

2. Methodology

The protocol was registered under International Prospective Register of Systematic Review (PROSPERO) on 1 Sept 2023 with the registration no. CRD42023456242.

2.1 Literature Search

The literature was systematically searched from 30 July 2023 to 1 Sept 2023 for all studies involving prediction models for the risk of developing diabetic retinopathy. Advanced search was conducted with the search string below in PubMed.

"Retinal Diseases"[Mesh] OR "Vision Disorders"[Mesh] OR blindness[tiab] OR retinopath*[tiab] OR vision impairmen* [tiab] OR visual impairmen* [tiab] OR vision disorder*[tiab] OR visual disorder*[tiab] AND predict*[tiab] NOT "Animals"[Mesh]. 1194 results were found from 30 July to 1 September 2023. There were only 841 results when search was restricted to recent 5 years, which was 2019.

Then, searching for relevant article was continued in Scopus, ScienceDirect, ProQuest, Web of Science database. In Scopus, 11 documents were found with the keyword of "machine learning technique for predicting risk of diabetic retinopathy". In ScienceDirect, 378 results were found using same keyword with the year begins at 2019 and refined to research articles. There were 78 results when advanced search was conducted where the keyword of "predicting risk of diabetic retinopathy" was placed at the column of title, abstract, or author-specified keyword since 2019. In ProQuest, there were 4069 results when entering the same keywords. Advanced search with the keyword "machine learning technique AND predicting risk of diabetic retinopathy" in anywhere, source of scholarly journal, document type of articles, and in English language, giving rise to 29 results. On the other hand, there were 10 results from Web of Science database.

2.2 CHARMS for Studies Selection

Manual filtering has been done for the search results and 10 main articles were selected for review following the guidance of CHecklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies (CHARMS) [9]. Studies were included when meeting the following criteria: (1) the prediction model was developed for patients with type I or type II diabetes mellitus (2) the outcome of the model was any stage of diabetic retinopathy. The studies were excluded if (1) patients of gestational diabetes or other special type of diabetes (2) patients were having other eye diseases that affect fundus examination (3) it was performed on animals. The potential relevance was examined when filtering through articles. Our main focus is to predict the risk from the clinical variables or risk factors other than from the fundus image.

2.3 PROBAST for Data Extraction for Quality Assurance

Risk of bias was assessed using the guidance of Prediction model risk Of Bias Assessment Tool (PROBAST) [9]. A combination of 3 reviewers independently reviewed each title, abstract and full text then extracted data from each article.

3. Results and Discussions

From CHARMS and PROBAST assessment, the 10 main articles selected for review are either in low risk of bias or unclear risk as depicted in Table 1. In Jo et al., [7] and Tsao et al., [8], the risk of bias and applicability in the context of participant are unclear because the inclusion and exclusion criteria for participants in not specifically mentioned in the paper.

Table 1
Summary of risk of bias and applicability assessment

Author, Year	Risk of Bias				Applicability			Overall	
	1. Participants	2. Predictors	3. Outcome	4. Analysis	1. Participants	2. Predictors	3. Outcome	**Risk of Bias**	**Applicability**
Gandhi et al., 2023	+	+	+	+	+	+	+	+	+
Jo et al., 2022	?	+	+	+	?	+	+	?	?
Zhao et al., 2022	+	+	+	+	+	+	+	+	+
Ke et al., 2023	+	+	+	+	+	+	+	+	+
Li et al., 2021	+	+	+	+	+	+	+	+	+
Yao et al., 2019	+	+	+	+	+	+	+	+	+
Liu et al., 2022	+	+	+	+	+	+	+	+	+
Tsao et al., 2018	?	+	+	+	?	+	+	?	?
Alfian et al., 2020	+	+	+	+	+	+	+	+	+

Homayouni et al., 2022	+	+	+	+	+	+	+	+	+

+	Low Risk of Bias	-	High Risk of Bias	?	Unclear

Table 2 tabulated the highlight of machine learning algorithms on diabetic retinopathy prediction together with input and output features. It consists of references, model of the study, datasets, participant detail, types and numbers of input predictor, statistical method, model development technique, outcome of prediction, model evaluation method and model performance.

Table 2
Machine learning algorithms on diabetic retinopathy prediction together with input and output features

References	Model	Datasets	Participant Detail	Input Predictors	No of input predictors	Statistical method	Model development technique	Outcome of prediction	Model evaluative method, Training: Testing Split	Model performance
Gandhi et al., 2023 [10]	web-based tool: DRRisk (https://drandml.cdrewu.edu/)	No: 40,631 Location: Los Angeles County Department Duration: January 1, 2015 - December 31, 2017	Age: 18 years of age or older Gender: 57.5 % of the individuals were women Type of Diabetes: T1DM & T2DM	Demographics: Age, Sex, Ethnicity Diabetes history: Duration of diabetes (years), Insulin dependence Clinical measurements: Systolic BP, Diastolic BP, Lab results: Hb, HbA1c, Blood urea nitrogen (BUN), Triglycerides Comorbidities:	14, 6 predictors are mandatory: Duration of Diabetes, Hb A1c, BUN, Sex, Ethnicity and Insulin Dependence	Univariate analysis	Deep neural network with Python flask web frame work	Risk category in percentages as: (1) low-risk DR: less than 25% risk, (2) moderate risk DR : 25% - 55% risk and (3) high risk DR: greater than 55% risk	10-fold cross-validation	AUC: 0.800 Sensitivity: 0.722 Specificity: 0.742

				Nephropathy, Neuropathy, Stroke						
Jo et al., 2022 [11]	Long-term prediction model	No: 52,927 Location: 6 referral hospitals in Korea Duration: January 2009 - July 2020	Age: 18 years of age or older Gender: about 52% were women Type of Diabetes: T2DM	Diabetes history: DM treatment duration, Clinical measurements: height, MAP, blood pressure Lab results: BUN, eGFR, glucose, AST, HbA1c Comorbidities: CVD	10	T-tests Chi-square test MATLAB	Support vector machine (SVM)	Occurrence of VTDR at 10-year	15-fold cross-validation	Accuracy: 0.700 Sensitivity: 0.958 Specificity: 0.664 F1 score: 0.810
Zhao et al., 2022 [12]	Prediction model for the risk of diabetic retinopathy (DR) in type 2 diabetes mellitus	No: 7943 Location: Department of endocrinology of Dalian Medical University with the Central Hospital of Dalian Duration: January 2010 - Septem	Age: ≥18 years Type of Diabetes: T2DM	Demographics: Age, Sex Diabetes history: Usage of different category of drugs, Duration of diabetes, Follow-up time Clinical measurements: BMI, BP Comorbidities: Hypertension Lab results: HbA1C, FBG, SUA, eGFR	18	Chi-square test, two-sample t-test, Two-tailed hypothesis testing R statistical and computing software version 4.0.2	Extreme Gradient Boosting (XGBoost)	Occurrence of DR at each follow-up time point in up to 10 years	5-fold cross-validation	AUC: 0.803 Accuracy: 0.889 Sensitivity: 0.740 Specificity: 0.811

		ber 2018.		and lipid profile: LDL-C, TC, TG,						
Ke et al., 2023 [13]	A nomogram for predicting vision-threatening diabetic retinopathy (VTDR) in type 2 diabetes mellitus (T2DM) with mild non-proliferative diabetic retinopathy (NPDR) patients	No: 440 Location: Centre for Endocrine Metabolism and Immune Diseases of Beijing Luhe Hospital, China Duration: October 2017 - April 2018	Age: >18 years Type of Diabetes: T2DM	Lab results: 2-h C-peptide, sural nerve conduction impaired (SNCI), urine albumin-to-creatinine ratio (UACR)	3	Kruskal–Wallis test chi-square test R software version 3.6.3	Least absolute shrinkage and selection operator (LASSO) method	calculate the individual risk for the progression of VTDR	Bootstrap, 70:30	AUC: 0.730 Sensitivity: 0.848 Specificity: 0.606
Li et al., 2021 [14]	Predictive model based on XGBoost	No: 32 452 Location: People's Liberation Army General Hospital Duration: 1 January 2013 - 31 December 2017	Age: not mentioned Type of Diabetes: T2DM	Demographic: age Diabetic history: insulin treatment Comorbidities: nephropathy, diabetic lower extremity arterial disease (DLEAD) Lab results: fasting blood glucose HbA1c,	17 variables	χ2 test t-test	XGBoost	DR risk prediction model based on Shapley Additive ex Planation (SHAP) method	10-fold cross validation	AUC: 0.900 Accuracy: 0.900 Sensitivity: 0.700 Specificity: 0.90

				total cholesterol, triglyceride, creatinine, urea, direct bilirubin, total protein and albumin, glutamine transferase, lactate dehydro-genase, haematology test like fibrinogen, prothrombin activity						
Yao et al., 2019 [15]	Back propagation artificial neural network (BP-ANN) model	No:530 Location: Fengyutan Health Center Duration: August - October 2011	Age: 18 years or older Type of Diabetes: T2DM	Diabetic history: duration of diabetes, family history of diabetes Clinical measurement: waist to hip ratio, Lab results: HbA1c	4	Unconditional Binary Logistic Regression, Multivariable Logistic Regression Statistical SPSS, Version 20.0, IBM	Back propagation artificial neural network (BP-ANN) toolbox Matlab 2010α version	DR risk prediction model	Training set, validation set and test set according to a ratio of 3:1:1	AUC: 0.840 Sensitivity: 0.730 Specificity:0.830 Youden index: 0.550
Liu et al., 2022 [16]	Prediction model based on the extreme learning machine (ELM)	No: 1309 Location: Lu'an Hospital of Anhui Medica	Age: not mentioned Type of Diabetes:	Demographics, Diabetic history, Clinical measurements, Lab results,	Not specifically mentioned	Not mentioned	Extreme Learning Machine	DR risk prediction model	10-fold cross-validation	AUC:0.883 Accuracy :0.845 Sensitivity: 0.679 Specificity: 0.932 Precision: 0.839

		l University in China Duration: January 1, 2020 - November 31, 2021	T2DM	Urine test						NPV: 0.846
Tsao et al,2018 [17]	Prediction model for DR in type 2 diabetes mellitus	No: 536 Location: Private hospital in northern Taiwan Duration: January 2012-December 2012	Age: ≥18 year	Demographic: age, gender, Diabetic history: duration of disease, family history of diabetes and insulin treatment Clinical Measurement: Systolic blood pressure (SBP), diastolic blood pressure (DPB), body mass index (BMI), self-monitoring blood glucose (SMBG), exercise,	10	chi-squared test, t-test	SVM	DR risk prediction model	Random Percentage Split 80:20	AUC: 0.839 Accuracy: 0.795 Sensitivity: 0.933 Specificity: 0.724
Alfian et al., 2020 [18]	DNN (Deep Neural Network) prediction model	No: 133 Location: Iran	Age: 16-79 Type of Diabe	Demographics: Age Diabetic history:	5	Not specifically mentioned	Deep neural network (DNN) with	DR risk prediction model	10-fold cross-validation	AUC: 0.804 Accuracy: 0.820 Sensitivity:

		Duration: (collectedby Khodadadi et al.)	tes: T1DM and T2DM	DM duration Lab results: FBS, HDL,HbA1c			Recursive feature elimination (RFE) Python V3.7.3, the Scikit-learn V0.22.2 library			0.760, Specificity: 0.804 F1 score 0.718
Homayouni et al., 2022 [19]	Prediction model using the Progressive Ablation Feature Selection (PAFS) method with XGBoost	No: 70,314 Location: Cerner Health Facts, United State Duration: 2020	Not mentioned	Demographics: Race, Comorbidities: Neuropathy, Nephropathy Lab results: Creatinine, Haematocrit, BUN, Albumin, Calcium, Sodium	9	Filter-based univariate	Progressive Ablation Feature Selection method with XGBoost Recursive feature elimination (RFE) Least absolute shrinkage and selection operator (LASSO) method	DR risk prediction model	10-fold Cross-Validation	AUC: 0.966

Further details can be found in the supplementary material where CHARMS and PROBAST template by Fernandez-Felix BM [9] is used. The key domain in the template is divided into study information, source of data, participants, outcome to be predicted, candidate predictors, sample size, missing data, model development, model performance, model evaluation, results, interpretation, and observation.

3.1 Classification of Retinopathy in Prediction Model

The basic of retinopathy classification in prediction models is based on International clinical diabetic retinopathy Disease Severity Scale and International Clinical Diabetic Macular Edema Disease Severity Scale[20].

Then, searching for relevant article was continued in Scopus, ScienceDirect, ProQuest, Web of Science database. In Scopus, 11 documents were found with the keyword of “machine learning technique for predicting risk of diabetic retinopathy”. In ScienceDirect, 378 results were found using same keyword with the year begins at 2019 and refined to research articles. There were 78 results when advanced search was conducted where the keyword of “predicting risk of diabetic retinopathy” was placed at the column of title, abstract, or author-specified keyword since 2019. In ProQuest, there were 4069 results when entering the same keywords. Advanced search with the keyword “machine learning technique AND predicting risk of diabetic retinopathy” in anywhere, source of scholarly journal, document type of articles, and in English language, giving rise to 29 results. On the other hand, there were 10 results from Web of Science database.

3.2 The Clinical Variables with Associated Datasets

The clinical variables are the input predictors for the prediction models. Many of the clinical variables are known risk factors for the incidence and progression of DR[21]. They affect the progression of DR and hence the result of the prediction. In this paper, they are divided into four categories which are demographic details, clinical measurements, history of diabetes and laboratory results as in Fig 1. The demographics details are age, gender, ethnicity; clinical measurements are systolic blood pressure (SBP), diastolic blood pressure (DPB), body mass index (BMI), waist to hip ratio; history of diabetes are the duration of diabetes, treatment or usage of different category of drugs; comorbidities such as nephropathy, neuropathy, cardiovascular disease and laboratory result including blood glucose, HbA1c, haematocrit, kidney and liver function test like serum creatinine, serum urea, albumin, calcium, sodium, direct bilirubin, total protein, albumin, glutamine transferase, lactate dehydrogenase, fibrinogen, prothrombin activity, lipid profile like total cholesterol, HDL, LDL and triglyceride, hematology test like fibrinogen and prothrombin activity, urine albumin-to-creatinine ratio (UACR), with latest research on 2-h C-peptide, sural nerve conduction impaired (SNCI)

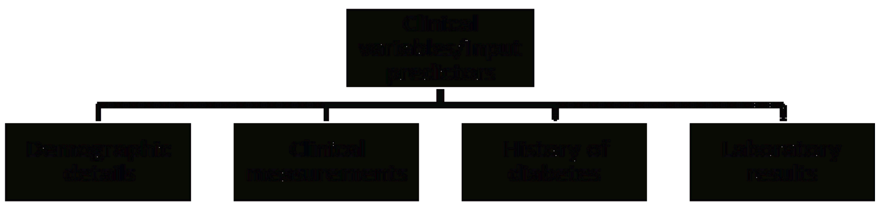

Fig. 1 Category of Clinical Variables/Input Predictors

3.3 The Prediction Models

The prediction models of different studies are based on different algorithms.

Support Vector Machine (SVM) has been employed by Jo et al., [11]. There are SVM for classification and regression and they are meant for more complex models not defined simply by hyperplanes. SVM allows for complex decision boundaries but it needs careful preprocessing of the data and fine tuning of the parameters. The important parameters are regularization parameter, C and gamma from radial basis function or Gaussian kernel.

Zhao et al., [12], Li et al., [14], and Homayouni et al., [19] used Extreme Gradient Boosting (XGBoost): It is an ensemble method which manage to adaptively change the distribution of the training examples to enhance the classification of harder example. However, it tends to overfit, resulting in poor generalization performance in some cases.

Other studies such as Yao et al., [15] and Alfian et al., [18] have implemented Artificial Neural Network (ANN) and Deep Neural Network (DNN) for predicting diabetic retinopathy from datasets. It is interesting to learn that Yao et al., [11] used back propagation which is simply a reverse mode automatic differentiation. The trick of reverse mode is that we started calculating the vector by multiplying a matrix rather than multiply large matrices initially for each layer before multiply by a vector. In this way, back propagation is cost-effective. On the other hand, DNN technique employed by Alfian et al., [18] because it is believed to have higher prediction accuracy.

The model by Homayouni et al., [19] has the highest area under AUC curve (AUC), which is 0.966 followed by Li et al., [14] which is 0.90. The two XGBoost models have outstanding ability to give prognosis on risk of DR. In the context of accuracy, the predictive model by Li et al., [14]provides the highest score 0.90 using XGBoost. Meanwhile, the SVM model by Jo et al., [11] has the most sensitivity level of 0.958, followed by Tsao et al., [17] of 0.933 using SVM model. Other than that, the highest score of specificity achieved by Liu et al., [16] which is 0.932. The model was built based on extreme learning machine (ELM).

3. Challenges And Future Works

We can see the challenges that most of the researches are facing by looking at the details of the papers to compare the strength and weaknesses of each model.

While it is hard to compare the classifiers' performances owing to the different characteristics of dataset and feature used, they have achieved satisfactory results in typical classification task. The feature engineering approaches can be seen to have achieved a stagnant progress owing to the fact most of the features are highly correlated. To make future progress, new discriminative features are necessary to enhance existing classifier performances. That needs contribution from the domain experts identifying clinical variables from their research. This makes some of the study like Ke et al., [13] used mostly only laboratory result as their predictors which might not be the real-life scenario where many other risk factors affect the risk of diabetic retinopathy. Nevertheless, it is expected that the advancement will be slow because clinical research usually requires lengthy time and large funding.

Deep learning neural networks are powerful and status quote for current machine learning landscape[4], but the lack of clinical data and the feature set have limited their usefulness for DR prediction task. One of the possible future directions is to use generative algorithms to generate new data points for classifier training.

XGBoost is a more recent algorithm that has achieved good results in previous studies compared with SVM[22]. Nevertheless, we do not expect to have critical breakthroughs in its performance due to the lack of dataset and new features. Future work can focus on using additional information or prior knowledge in the design on the classifier. For instance, clinic information can be embedded in the probability function that will bias the prediction on certain examples in the dataset.

Another important challenge to be noticed is that the process of embedding a machine learning model into an application has not been emphasized enough in most of the study. There is only one good web-based tool: DRRisk by Gandhi et al., [10] based on current finding. It is vital to have interaction interface of this web-based tool or application for the use of layman for calculating the risk themselves thus predicting their follow-up intervals.

In short, each model has their own capability in predicting the risk of developing DR. The suitability of each model would depend on the population measured. The future work includes combination with image processing and analysis of fundus images of the patients then identification of the area that is possible to develop diabetic retinopathy. In the future, we should be able to detect the area of fundus that is prone for lesion of diabetic retinopathy.

4. Conclusions

Many countries have one to two yearly eye screening programs for patients with diabetes to ensure early detection and treatment. However, the frequency might be too high for lower risk group. The healthcare system is also unsustainable in certain developing countries due to growing prevalence of diabetes[23]. Hence, the development of more efficient models in predicting risk of retinopathy are vital to ensure correct interval of following up in ophthalmology clinic.

Acknowledgement
We would like to thank Universiti Malaysia Sarawak for supporting this work. This research was not funded by any grant.

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