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Original Research

Iranian Risk Model as a Predictive Tool for Retinopathy in Patients with Type 2 Diabetes

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ABSTRACT

Objective: Diabetic retinopathy (DR) is the leading cause of blindness in patients with type 1 or type 2 diabetes. The gold standard for the detection of DR requires expensive equipment. This study was undertaken to develop a simple and practical scoring system to predict the probability of DR.
Methods: A total of 1782 patients who had first-degree relatives with type II diabetes were selected. Eye examinations were performed by an expert ophthalmologist. Biochemical and anthropometric predictors of DR were measured. Logistic regression was used to develop a statistical model that can be used to predict DR. Goodness of fit was examined using the Hosmer-Lemeshow test and the area under the receiver operating characteristic (ROC) curve.
Results: The risk model demonstrated good calibration and discrimination (ROC area=0.76) in the validation sample. Factors associated with DR in our model were duration of diabetes (odds ratio [OR]=2.14, confidence interval [CI] 95%=1.87 to 2.45); glycated hemoglobin (A1C) (OR=1.21, CI 95%=1.13 to 1.30); fasting plasma glucose (OR=1.83, CI 95%=1.28 to 2.62); systolic blood pressure (OR=1.01, CI 95%= 1.00 to 1.02); and proteinuria (OR=1.37, CI 95%=1.01 to 1.85). The only factor that had a protective effect against DR were body mass index and education level (OR=0.95, CI 95%=0.92 to 0.98).
Conclusions: The good performance of our risk model suggests that it may be a useful risk-prediction tool for DR. It consisted of the positive predictors like A1C, diabetes duration, sex (male), fasting plasma glucose, systolic blood pressure and proteinuria, as well as negative risk factors like body mass index and education level.

Mots clés :
rétinopathie diabétique
facteurs de risque
diabète de type 2

RÉSUMÉ

Objectif : La rétinopathie diabétique (RD) est la cause principale de cécité des patients souffrant de diabète de type 1 ou de type 2. Le critère de référence de la détection de la RD exige du matériel coûteux. Cette étude a été entreprise pour élaborer un système de notation simple et pratique pour prédire la probabilité de RD.
Méthodes : Un total de 1782 patients qui avaient de la famille de premier degré qui souffrait de diabète de type II ont été sélectionnés. Des examens ophtalmologiques ont été réalisés par un ophtalmologiste spécialisé. Les prédicteurs biochimiques et anthropométriques de la RD ont été mesurés. La régression logistique a été utilisée pour élaborer un modèle statistique qui peut être utilisé pour prédire la RD. La validité de l'ajustement a été examinée à l'aide du test de Hosmer et Lemeshow et de la surface sous la courbe caractéristique d'efficacité du récepteur (ROC).
Résultats : Le modèle de risque a démontré un bon étalonnage et une bonne discrimination (surface ROC = 0,76) dans l'échantillon de validation. Dans notre modèle, les facteurs associés à la RD étaient la durée du diabète (ratio d'incidence approché [RIA] = 2,14, intervalle de confiance [IC] à 95 % = 1,87 à

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2,45), l'hémoglobine glyquée (A1c; RIA = 1,21, IC à 95 % = 1,13 à 1,30), la glycémie veineuse à jeun (RIA = 1,83, IC à 95 % = 1,28 à 2,62), la pression artérielle systolique (RIA= 1,01, IC à 95 % = 1,00 à 1,02) et la protéinurie (RIA = 1,37, IC à 95 % = 1,01 à 1,85). Le seul facteur qui a eu un effet protecteur contre la RD était l'indice de masse corporelle et le niveau d'instruction (RIA = 0,95, IC à 95 % = 0,92 à 0,98).
Conclusions : La bonne performance de notre modèle de risque montre qu'il peut être un outil de prédiction du risque utile de RD. Il comprenait les prédicteurs positifs tels que l'A1c, la durée du diabète, le sexe (masculin), la glycémie veineuse à jeun, la pression artérielle systolique et la protéinurie, ainsi que les facteurs de risque négatifs tels que l'indice de masse corporelle et le niveau d'instruction.

Introduction

Diabetes mellitus is a health problem that affects an estimated 150 million people in the world and is expected to affect 200 million people by 2025. The most common effect of diabetes is diabetic retinopathy (DR) (1). DR is a well-known diabetic complication that is commonly associated with poorly controlled diabetes. According to recent research, DR has become the leading cause of blindness and visual impairment in adults younger than 40 years of age in developed countries (2). A systematic review revealed that the prevalence of DR is 34.6% (3). It has been estimated that the number of patients with DR will become 1.5 times greater by 2030. In southeast Asia and the western Pacific regions, diabetic retinopathy accounts for 3% to 7% of all cases of blindness (4). It is important for the healthcare system to diagnose patients at risk for developing DR. The significance of screening has been highlighted by numerous researchers. They have found that early detections of vision-threatening retinopathy by means of consistent fundus analysis is the solution for decreasing visual loss and blindness and for anticipating the course of disease in people with diabetes (5,6). The current gold standard for the detection of DR is fundus photography, which requires expensive equipment (7). However, even in countries with facilities for close monitoring of diabetes, no consensus exists concerning the cost-effectiveness of reliable methods of screening for DR (8). In other words, although multiple screening tools are used to detect DR, the majority of them are invasive and costly. Numerous DR risk factors have been reported, such as diabetes duration, hyperglycemia, insulin therapy, high blood pressure, nutritional and genetic factors, pregnancy and hyperlipidemia (9–11).

This study was designed to develop a simple risk score model intended to predict retinopathy in patients with type 2 diabetes.

Methods

Participants

This cross-sectional study was carried out in 1782 patients with first-degree relatives who had type 2 diabetes. They were chosen from patients attending an outpatient clinic of the Isfahan Endocrinology and Metabolism Research Centre in Isfahan, Iran. This study was conducted within the Isfahan Diabetes Prevention Study framework (12). The Isfahan Diabetes Prevention Study is an ongoing cohort study begun in 2003. It aims to investigate the efficacy of diet and physical activity in decelerating the rate of type 2 diabetes. Patients younger than 30 years of age and those without histories of diabetes in first-degree relatives were excluded. After informed consent was obtained, the demographic characteristics of patients were collected through a questionnaire. Those with fasting plasma glucose (FPG) levels $\geq$7 mmol/L and 2-hour plasma glucose levels $\geq$11.1 mmol/L were considered to have diabetes and were included in the present study. All procedures followed were in accordance with the ethical standards of the Research Council of Endocrine and Metabolism Research Center of Isfahan University of Medical Science and with the 1975 Declaration of Helsinki.

Assessment of diabetic retinopathy

The presence of DR was evaluated by 1 experienced ophthalmologist using Goldmann applanation tonometry and indirect ophthalmoscopy. Biomicroscopic examination of the anterior segment and lens opacity and intraocular pressure measurements were carried out to detect the presence or absence of DR. The diagnosis of DR was established on the basis of the following indicators: microaneurysms, hard exudates, cotton-wool spots, retinal hemorrhages, proliferative diabetic retinopathy, extensive neovascularization, vitreous hemorrhages and fibrovascular proliferation.

DR was determined annually by an expert ophthalmologist in all centres by means of the international diabetic retinopathy and diabetic macular edema disease scales, with small changes. We classified retinopathy into 4 stages: stage 0, no retinopathy; stage 1, hard exudates and hemorrhage; stage 2, soft exudates; stage 3, venous changes, including beading, loop and duplication, and intraretinal microvascular abnormalities; and stage 4, new vessels, vitreous hemorrhage, fibrous proliferation and retinal detachment. Retinopathy was considered as progression beyond stage 2.

Anthropometric assessment

The weights and heights of patients were obtained following standard procedures, in which they were wearing light clothes and not wearing shoes. Weights and heights were recorded to the nearest 0.1 kg and 0.5 cm, respectively. Body mass indexes (BMIs) were calculated by dividing weight in kilograms by the square of height in meters. BMIs $\geq$25 kg/m^2 were considered to be a negative indicator for DR.

Biochemical and blood pressure assessment

Systolic blood pressures (SBP) and diastolic blood pressures (DBP) were taken after 15 minutes of rest in the sitting position by using a mercury sphygmomanometer. Subject were asked to abstain from smoking, extreme physical activity and drinking tea or coffee before their blood pressures were measured. Blood pressure $\geq$130/85 mm Hg was considered a negative indicator for DR.

Blood samples were taken after overnight fasting. FPG, serum triglyceride (TG), total cholesterol (TC) and high-density lipoprotein cholesterol levels were determined by using an enzymatic method (Chem Enzyme, Pars Azmoon Company, Tehran, Iran). Low-density lipoprotein cholesterol levels were calculated using the Fried-Wald formula in patients with TG $<$400 mg/dL. Glycolated hemoglobin (A1C) was measured by ion-exchange chromatography. Protein in urine was determined by using the trichloroacetic acid method and an auto analyzer (BT 3000, Pars Azmoon company, Tehran, Iran). Proteinuria was defined as $\geq$1.0 g/g. Blood urea nitrogen (BUN) was measured by standard urease assay/conductivity and creatinine with picric acid reactions. All experiment procedures were performed in the central laboratory of the Isfahan Endocrine and Metabolism Research Centre.

Finally, diabetic retinopathy risk factors in the present study were as follows: sex, age, diabetes duration, education, smoking,

history of blood pressure, history family of diabetes, BMI, A1C, FPG, TC, TG, LDL, HDL, BUN, creatinine, protein and blood pressure.

Statistical analysis

All subjects with missing values for the outcome variables (presence or absence of DR) were excluded from the analysis. Any missing predictor (risk factor) values were imputed using the imputation by chained equations (ICE) procedure in STATA 10 (13). The dataset was then split randomly into 2 parts: 80% was used for model development and 20% for model validation. The model was developed using logistic regression with backward elimination at the 5% level. The Hosmer-Lemeshow goodness-of-fit test (14) was used to assess both the goodness of the model fitness in data development and its calibration in data validation. The receiver operating characteristic (ROC) area was calculated to assess the discrimination of the model. Finally, the data were recombined to refit the final risk model. The regression coefficients from this model were scaled and rounded to provide a simplified risk formula.

The Harrell rule of 10 (15,16) was used to predict the required sample size. The events per variable (EPVs) were calculated. The EPVs are the ratio of the number of outcome events to the number of predictor variables. If the EPVs exceed 10, it suggests that the estimated regression coefficients and their confidence intervals are reliable (17,18). Because this dataset contained 1019 patients with DR and 763 without DR, this EPV threshold was easily exceeded.

Results

We included 1782 patients with diabetes in the analysis, 1019 of whom had a DR event. Descriptive statistics of demographic and biochemical characteristics are shown in Table 1. Continuous and categoric variables are presented as mean ± SD and number (%), respectively; 32.7% of patients were males and 67.3% were females. The age range of the participants was 30 to 84 years (mean age, 50.3 years). As is shown in Table 2, univariate complete-case analyses were performed on the whole dataset after applying multiple imputations so as to examine the potential prognostic ability of the predictors. Age, duration of diabetes, history of BP, hypertension, SBP, DBP, A1C, FPG, BUN and proteinuria significantly increased the risk for DR, and BMI and education levels significantly decreased the risk for DR.

Model development

All subjects with missing outcome values (presence or absence of DR) were excluded from the analysis. The development dataset contained 1429 subjects, 805 (56.3%) of whom had diabetic retinopathy. Table 3 shows the results of fitting a multivariable logistic regression model, with backward elimination. These results were obtained by combining 5 imputed datasets using Rubin rules. Backward elimination at the 5% significance level removed log (DBP) (p=0.90); log (LDL) (p=0.85); history of BP (p=0.84); cholesterol (p=0.76); log (TG) (p=0.65); family history (p=0.60); log (HDL) (p=0.34); log (creatinine) (p=0.35); BP (p=0.18); smoking (p=0.17) and log (BUN) (p=0.14). Age and sex were kept in the model regardless of their statistical significance. The Hosmer-Lemeshow test and corresponding plot (results not shown) suggested excellent agreement between the observed and predicted risks in model development (p=0.65; 8 degrees of freedom [df]).

Model validation

The validated data contained 1429 subjects, 805 (56.3%) of whom had diabetic retinopathy. The Hosmer-Lemeshow test was used again to assess the fit of the risk model (Figure 1). It suggested a very good agreement between the observed and predicted risks (p=1.00; 10 df). In particular, there was an excellent agreement between the total observed (214) and the predicted cases of retinopathy (208.4). The ROC area was used to quantify the discrimination of the model and produced a value of 0.76 (95% CI 0.71 to 0.81).

Table 1
Descriptive analysis for variables that recorded for patients with diabetic retinopathy

Variables	Mean ± SD or n (%)
Sex	
Male	583 (32/7%)
Female	1199 (67.3%)
Age (years)	50.3±9.6
Duration (year)	5.8±5.9
BMI (kg/m^2)	27.9±4.4
Family history of diabetes	1268 (72.8%)
History of BP	503 (31.9%)
Hypertension	1577 (88.8%)
SBP (mm Hg)	121.3±18.7
DBP (mm Hg)	74.7±11.1
A1C (%)	9.1±2.3
FPG (mg/dL)	197.5±77.5
Total cholesterol (mg/dL)	221.1±49.4
TG (mg/dL)	221.7±142.7
LDL (mg/dL)	136.1±41.4
Creatinine (mg/dL)	0.9±0.8
BUN (mg/dL)	25.4±9.2
Proteinuria	643 (44%)
Current smoking	147 (9.5%)
Education	
None	451 (26.5%)
Low	766 (45%)
Primary	143 (8.4%)
Secondary	215 (12.6%)
University	128 (7.5%)

A1C, Glycated hemoglobin; *BMI*, body mass index; *BP*, blood pressure; *BUN*, blood urea nitrogen; *DBP*, diastolic blood pressure; *FPG*, fasting plasma glucose; *LDL*, low-density lipoprotein; *SBP*, systolic blood pressure.

Table 2
Univariate analysis of predictors

Variables	Odds ratio (CI 95%)	p value
Sex		
Male	1	0.072
Female	0.83 (0.68 to 1.02)	
Age (years)	1.03 (1.02 to 1.04)	<0.001
Log duration (year)	2.24 (2.00 to 2.50)	<0.001
BMI (kg/m^2)	0.95 (0.93 to 0.97)	<0.001
Family history of diabetes	1.00 (0.81 to 1.24)	0.99
History of BP	1.30 (1.05 to 1.62)	0.017
Hypertension	1.90 (1.41 to 2.56)	<0.001
SBP (mm Hg)	1.01 (1.00 to 1.01)	<0.001
DBP (mm Hg)	1.01 (1.00 to 1.02)	0.004
A1C (%)	1.29 (1.22 to 1.36)	<0.001
Log FPG	3.21 (2.44 to 4.21)	<0.001
Total cholesterol (mg/dL)	1.00 (0.99 to 1.00)	0.45
Log TG	1.01 (0.85 to 1.21)	0.87
Log LDL	0.95 (0.64 to 1.42)	0.82
Log HDL	1.26 (0.75 to 2.11)	0.38
Log creatinine	1.32 (0.99 to 1.75)	0.056
Log BUN	1.48 (1.16 to 1.89)	0.001
Proteinuria	1.39 (1.13 to 1.72)	0.002
Current smoker	1.35 (0.94 to 1.93)	0.099
Education		
None	1	<0.001
Low	0.66 (0.52 to 0.84)	
Primary	0.51 (0.35 to 0.75)	
Secondary	0.35 (0.25 to 0.49)	
University	0.37 (0.25 to 0.56)	

A1C, Glycated hemoglobin; *BMI*, body mass index; *BP*, blood pressure; *BUN*, blood urea nitrogen; *DBP*, diastolic blood pressure; *FPG*, fasting plasma glucose; *HDL*, high-density lipoprotein; *LDL*, low-density lipoprotein; *SBP*, systolic blood pressure; *TG*, triglyceride.

Table 3
Multivariable analyses for initial model

Predictors	Odds ratio (CI 95%)	p value
Sex		
Male	1	
Female	0.76 (0.57 to 1.02)	0.07
Age (years)	0.99 (0.97 to 1.00)	0.33
Log duration (year)	2.14 (1.87 to 2.45)	<0.001
BMI (kg/m^2)	0.95 (0.92 to 0.98)	0.001
SBP (mm Hg)	1.01 (1.00 to 1.02)	<0.001
A1C (%)	1.21 (1.13 to 1.30)	<0.001
Log FPG	1.83 (1.28 to 2.62)	0.001
Proteinuria	1.37 (1.01 to 1.85)	0.04
Education		
None	1	<0.001
Low	0.65 (0.47 to 0.90)	
Primary	0.50 (0.29 to 0.85)	
Secondary	0.30 (0.18 to 0.49)	
University	0.36 (0.20 to 0.63)	

A1C, Glycated hemoglobin; *BMI*, body mass index; *FPG*, fasting plasma glucose; *SBP*, systolic blood pressure.

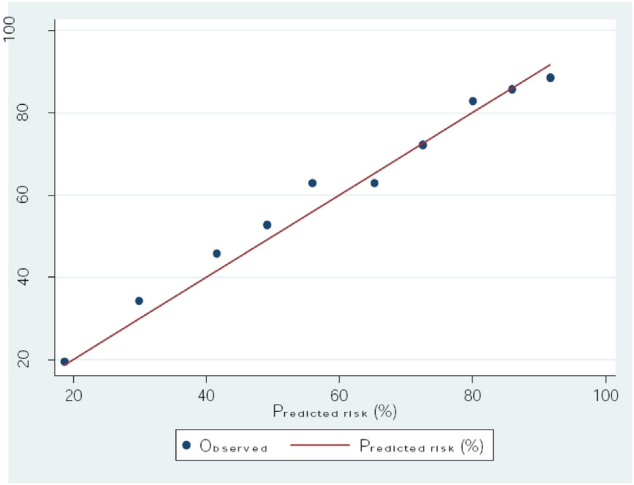

Figure 1. Plot for Hosmer-Lemeshow test in the validation data.

Risk model

The development and validation datasets were then recombined and the risk model refitted. This produced the following equation: π=probability of DR, which might be used to make predictions.

As a final step, a simplified version of the model was obtained by scaling and rounding the regression coefficients (Table 4). Note that age was removed from our model because all its risk scores were zero. To obtain a risk prediction, one adds the relevant scores together and then applies the following formula:

$$\begin{aligned}\text{Log}\ (\pi/1-\pi) \ = \ & -4.930 \text{ to } 0.00203 \times \text{age} - 0.382 \\ & \times \text{sex}\ [\text{female}] + 0.749 \times \log\ (\text{duration}) \\ & - 0.0452 \times \text{BMI} + 0.186 \times \text{A1C\_first} \\ & + 0.553 \times \log\ (\text{FPG}) + 0.0142 \times \text{SBP} \\ & + 0.275 \times \text{protein}\ [\text{yes}] - 0.431 \\ & \times \text{education}\ [\text{low}] - 0.679 \\ & \times \text{education}[\text{primary}] - 1.170 \\ & \times \text{education}[\text{secondary}] - 1.169 \\ & \times \text{education}[\text{university}].\end{aligned}$$

$$\text{RISK} \ = \ 100.\ (1 + \exp\ (3.03 - 0.232.\text{SCORE})) - 1$$

Alternatively, one could use the plot in Figure 2.

Discussion

In this study, the Diabetic Retinopathy Risk Score was designed as a predictive tool for identifying patients with type 2 diabetes in Isfahan, Iran, who are at high risk for DR. We found some criteria and parameters that could play roles in the development of retinopathy. These factors are summarized in Table 3. Some studies have shown that older adults have higher risks for DR (19), but others have reported that the risk for retinopathy in patients younger than 40 years of age were higher than those for patients 40 years of age or older (20). In our model, duration of disease was the significant predictor of DR development. Similar to a few studies (21–23), we found that the overall occurrence of retinopathy was 17% in persons having diabetes for fewer than 5 years and was 97.5% in those having diabetes for 15 years or longer. Compared to previous reports, the prevalence of DR was higher in our sample (24,25). Diabetes duration of 5 to 10 years was related to increased risk for DR (26,27), but most researchers have demonstrated that duration of more than 10 years predicts DR best. The reason is that longer duration equals longer exposure to hyperglycemia (20).

We examined the correlation between DR prevalence and sex of patients. Progression of retinopathy was more prevalent in males compared to females, and males were more vulnerable to DR. Similar observation have been reported in the past (28,29).

Another observation in our study was that higher A1C levels predicted DR well. It demonstrated a 35% reduction in microvascular problems by means of a 1% reduction in A1C (30,31). A systematic review suggested that glycemic control as evaluated by A1C is associated with decreased risk for DR (32). In contrast, in a study of patients with diabetes in Tehran province, Iran, A1C was not a significant risk factor for DR (26). What is clear is that hyperglycemia is a major risk factor for the development of DR (33–35).

According to our findings, BMI had an inverse association with DR. Evidence of the relationship between obesity and progression of DR are mixed, some showing a positive association (11,36–39). The differences in results could be due to the diversities in methodologies, study participants, sample sizes and anthropometric measurements. The underlying mechanisms of the relationship between BMI and DR remain largely unknown and need further investigation (37).

Levels of SBP have also been found to be associated with the severity of DR. As some studies, such as the UK Prospective Diabetes Study Group (UKPDS) reported, patients who have controlled their blood pressure had 34% and 47% reductions in the progression and deterioration of sight acuteness, respectively (40). Javadi et al (26) showed that hypertension was a significant risk factor for DR in the Tehranian population. Other studies have reported that increasing levels of BP were significantly associated with prevalence of DR (41).

Although triglyceride and cholesterol levels were risk factors for DR, they did not predict the occurrence of retinopathy in the present model. The association between lipid profiles and the pathogenesis of DR has been less well defined. In agreement with some studies, Benarous et al (42–44) did not find any association between serum lipids and the presence of DR. However, some studies have suggested that lowering blood lipids may be correlated with a decreased incidence of DR (45,46). Haddad et al (20) showed that plasma cholesterol and triglyceride concentrations were positively associated with DR.

In our study, proteinuria was a predictor of DR; however, BUN and creatinine were not. A Chinese study showed that albuminuria

Table 4
Risk scores for each predictor

Predictors	Categories	Score
Sex	Male	2
Duration (years)		
	2 to 4	3
	5 to 9	6
	10 +	8
BMI (kg/m^2)		
	<20	4
	20 to 24.99	3
	25 to 29.99	2
	30 to 34.99	1
SBP (mm Hg)		
	110 to 129.99	1
	130 to 149.99	2
	150+	4
A1C (%)		
	7 to 8.99	1
	9 to 10.99	3
	11+	5
FPG (mg/dL)		
	150 to 199	1
	200 to 299	2
	300 +	3
Proteinuria		1
Education		
	None	5
	Low	3
	Primary	2

A1C, Glycated hemoglobin; *BMI*, body mass index; *FPG*, fasting plasma glucose; *SBP*, systolic blood pressure.

is an independent risk factor for DR in patients with type 2 diabetes (42). Other studies have confirmed these findings (6,20,47,48).

A study of Japanese patients diagnosed with type 2 diabetes revealed that some variables, including sex, age, A1C levels (years after diagnosis), BMI, SBP, non-high-density lipoprotein cholesterol, albumin-to-creatinine ratio, current smoking and physical inactivity can be considered risk factors for the macro- and microvascular complications of diabetes (49). Constable et al reported that duration of diabetes is the most important predictive factor for DR (50).

The strength of our study is that it focuses on predicting DR based on several risk factors that are easy to obtain via noninvasive methods. But there are also some limitations, too. This is an Iranian cohort, and the model may not be applicable to other populations with DR; thus, this study needs to be repeated in other populations. The model designed in our study is not intended to be used as a screening tool because it identifies only the relative importance of risk factors for DR in Iranians with diabetes. It was developed as a simple and practical scoring system to predict the risk for DR in Iranians.

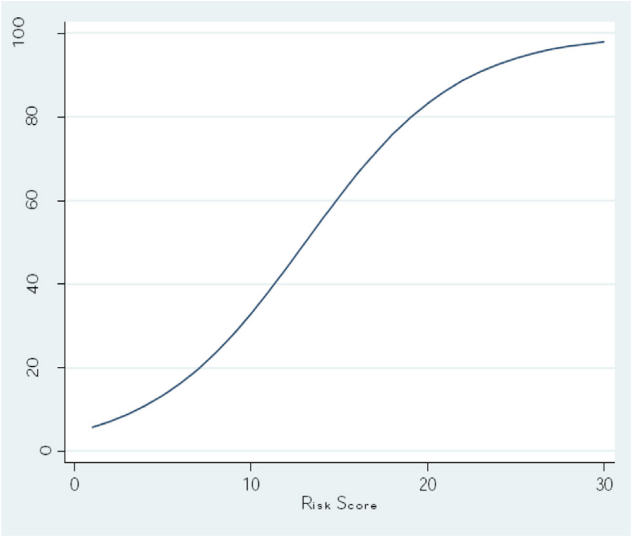

Figure 2. Total risk scores to risk (%) conversion.

In conclusion, the good performance of our risk model suggests that it may be a useful risk-prediction tool for the occurrence of DR. The interpretation of an individual's DR risk can be declared with relative precision. It consists of the positive predictors, such as A1C levels, duration of diabetes, sex (male), FPG, SBP and proteinuria, as well as negative risk factors such as BMIs and education levels.

Author Disclosures

All authors declare that there are no conflicts of interest. All procedures followed were in accordance with the ethical standards of the Research Council of Endocrine and Metabolism Research Center (EMRC) of Isfahan University of Medical Science and with the 1975 Declaration of Helsinki.

Author Contributions

GA, RO and MA designed the study; GA, RO and SMH conducted the analysis and interpreted the results; FAS and MHB drafted the manuscript; and GA, RO and SMH critically revised it. All authors approved the final version.

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