A Simple Scoring Scale for Predicting the Risk of Diabetic Retinopathy over 50 years old in China

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Abstract

Purpose

To construct and evaluate a simple scoring scale for predicting the risk of diabetic retinopathy (DR).

Methods

Based on the chronic disease management database of Yancheng City, Jiangsu Province, China, 1896 diagnosed patients over the age of 50 with diabetes were randomly selected and subjected to the self-designed epidemiological questionnaire survey and ocular clinical examination. Single-factor and multi-factor logistic regression analysis was used to screen the relevant influencing factors of DR and then according to the reference value principle, the weights were assigned, and a simple scoring scale was constructed. A receiver operating characteristic curve (ROC) was developed and the accuracy and validity of the simple scale were evaluated.

Results

The DR detection rate was 34.8 %. Multivariate analysis showed that family history of diabetes (odds ratio [OR]: 1.322, 95 % confidence interval [CI]: 1.012-1.727), diabetes treatment method (OR: 2.074, 95 % CI: 1.696-2.537), diabetes duration (OR: 1.113, 95 % CI: 1.089-1.138), and hemoglobin (Hb)A1c (OR: 1.276, 95 % CI: 1.099-1.482) were

independent DR risk factors. After excluding confounding factors and based on the β coefficient of the multivariate logistic analysis, the scale had a maximum score of 12 points. The area under the receiver operating characteristic curve was 0.753, the cut-off value was 4, the sensitivity was 66.5 %, and the coincidence rate was 70.9 %. To improve sensitivity, the cut-off value was lowered to 3; the sensitivity was 79.7 %, and the coincidence rate was 65.0 %.

Conclusion

The simple scale had good sensitivity and the ability to identify DR patients.

Introduction

Introduction

Diabetes mellitus (DM) is one of the world's fastest-growing chronic diseases and a leading cause of acquired vision loss.[1] The World Health Organization estimates that the total number of people with diabetes will double, from 171 million in 2000 to 366 million by 2030.[2] Diabetic retinopathy (DR), the primary retinal vascular complication of DM, remains the leading cause of acquired vision loss worldwide in the working-age population.[3-5] With the increasing number of people with diabetes, the number of DR and vision-threatening DR cases, including severe non-proliferative DR, proliferative DR, and diabetic macular edema (DME), is estimated to rise to 191.0 million and 56.3 million globally, respectively, by 2030.[6] China, like many countries, has seen a marked increase in the prevalence of DM. As of 2016, the number of DM patients exceeded 140 million, and the proportion of people over age 50 exceeded 90 %. It is estimated that over 60 million people in China will have DM by the year 2030.[7-9] About one-third of patients with diabetes suffer from DR[7]; therefore, the number of DR patients in China will surge to 18 million, seriously affecting the visual function of diabetic patients.[9]

In the early course of the disease, DR is generally asymptomatic. If left untreated, DR can seriously impair vision, eventually progressing to blindness.[1,4] Apart from the devastating visual effects that could lead to

reduced mobility, depression, and lower quality of life, DR is also associated with a higher risk of systemic vascular complications, imposing a noteworthy burden on individuals, households, communities, and societies.[10-11] Therefore, as a progressive disease, the early detection of DR and optimal DM management increases the chance of visual improvement and decreases the DME incidence rate.[12-13]

Studies have shown that although more than 80 % of diabetic patients were aware of the effects of diabetes on their eyes, only a small percentage of patients had regular fundus examinations.[14-16] In China, patients with diabetes usually see a doctor in the endocrinology department of the hospital first, but a fundus examination should be performed in the ophthalmology department. Patients' motivation to undergo retinal assessment is poor, hindering early diagnosis and management. Thus, designing a simple DR screening tool suitable for doctors in the clinic is essential to improve the early DR detection rate. A simple scale is practical in the primary public health environment because it is convenient, non-invasive, and low-cost.[17-18]

This study combined several conventional clinical indicators for DR patients and assigned them weighted values to simplify the statistical equation model and construct a simple scoring scale for DR screening. Consequently, the DR risk in diabetes patients can be quantified to guide

clinical practice.

Methods

Sample Size Calculation and Participant Recruitment

The sample size was calculated using the following formula:

$$n = z^2_{1\text{-}a/2} \times p(1 - p)/d^2$$

In this formula, $z^2_{1\text{-}a/2} = 1.96 \approx 2$ at 5 % type I error, p (the prevalence of DR among Chinese diabetic patients) was approximately 27.9 %,[9] and d (the absolute error or precision) was 10 % of p in our study, and the sample size was corrected by a sampling effect coefficient of 2.0. Therefore, the minimum sample size was approximately 2067.

$$n = 400 \times \frac{q}{p} \times 2 = 400 \times \frac{0.721}{0.279} \times 2 \approx 2067$$

In March 2019, 2067 patients over 50 years old with confirmed primary diabetes were randomly selected from the chronic disease management system of Yancheng City, Jiangsu Province. In total, 1965 people were chosen after verification by the local village committee, 102 people failed to be investigated because they had been away from the investigation points for more than 6 months. Sixty-nine subjects declined to participate in or withdrew from the survey or test or could not obtain clear fundus photographs were excluded, with 1896 subjects included in the analysis. Patients under 50-years-old were not included because of their high

mobility due to work-life factors and the inability to cooperate with epidemiological investigations and ophthalmic examinations.

The investigation followed the principles of research concerning human beings outlined in the Declaration of Helsinki and was approved by the Ethics Committee of the Affiliated Hospital of Nantong University (Approval No. 2019071). All participants signed written informed consent before the investigation began.

Data Collection

One month before the formal investigation, an ophthalmologist from the Affiliated Hospital of Nantong University trained the Funing County Center for Disease Control field workers on the purpose, procedure, and method of our investigation. A trained investigator interviewed each participant using self-designed questionnaires and collected information on demographic data (e.g., sex, age, and education level), living habits (e.g., smoking, drinking, and cell-phone use), diseases history (e.g., hypertension and hyperlipidemia), and diabetes-related data (e.g., family diabetes history, diabetes duration, treatment and control measures, and complications). The information on duration of diabetes and treatment collected was based on patients' existing records from the chronic disease management system of Yancheng City, Jiangsu Province. There

are three steps taken to ensure accuracy of the collected data: (1) The diagnosis and treatment information of diabetes are filled in the electronic case by clinicians in tertiary hospitals and above. (2) The information in the electronic cases need to be checked by the staff in the hospital medical record room and uploaded to the chronic disease management system. (3) The medical records uploaded to the chronic disease management system are checked and managed daily by the CDC (Center for Disease Control and Prevention) staff. There was also a physical examination (e.g., weight, height, blood pressure, blood glucose, and hemoglobinA1c [HbA1c]) and an ophthalmologic examination (e.g., the eyelid, conjunctiva, cornea, pupil, and lens) with a slit lamp microscope (YZ5T; Liu Liu, China). The intraocular pressure was measured with a non-contact tonometer (Keeler-Pulsair Intellipuff; Keeler Ltd., Windsor, England).

Variable Definitions

DR was diagnosed by an eye specialist in the Affiliated Hospital of Nantong University according to the Guidelines for Image Acquisition and Film Reading of Screening for Diabetic Retinopathy in China (2017).[19] The fundus images were all acquired after pupillary dilation. DR was graded for into 4 levels (NPDR I, NPDR Ⅱ, NPDR Ⅲ, PDR) according

to the severity. If any eye was identified as any level of DR, we will diagnose this patient as DR. Hypertension was diagnosed in the hospital or in the field examination, if the participant had a mean systolic blood pressure of ⩾140 mm Hg or diastolic blood pressure of ⩾90 mm Hg. Hyperlipidemia, diabetic nephropathy, and diabetic foot were diagnosed in the hospital. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m^2).

Statistical Analyses

SPSS 24.0 software package was used for statistical analysis of the data. All tests were bilateral, and the test level was $a = 0.05$.

Screening for Influencing DR Factors

For univariate analysis, the counting data were expressed as percentages (%), and a chi-square test was used to compare the two groups. Variables with statistical significance in the univariate analysis ($P < 0.05$) were included in the multivariate analysis. The logistic regression stepwise regression method (the forward likelihood ratio [LR] method) was used to adjust for potential confounding factors. The variables were gradually introduced using the partial maximum likelihood estimation to generate the final regression model until all variables were included. Each variable

in the model was statistically significant, and the statistical equation model for predicting DR was established. Then, the statistical equation model was simplified, and the simple scoring scale was constructed based on the weight of the final inclusion factors in the multi-factor statistical equation model.

Constructing a Simple Scoring Scale for DR

The simple scoring scale was constructed based on the scoring system method created by Sullivan, Massaro and Agostino[20-21] which uses β coefficients in the final multi-factor logistic regression equation as the scoring basis, gives different scores based on the weight of each risk factor in the final regression equation, and takes the total weighted scores as the overall score. These steps simplify the complex mathematical-statistical model, making it clinically practical.

Scoring Scale Evaluation

The constructed scoring scale was comprehensively evaluated from two validity and reliability aspects. A receiver operating characteristic curve (ROC) was used for scale discrimination. All patients were scored according to the constructed scoring scale; the total score of each patient was used as a test variable, and the actual follow-up prognosis of patients

was used as a state variable. A ROC curve were drawn to comprehensively evaluate the scoring scale. Combined with the area under the ROC curve (AUC), the sensitivity, specificity, and diagnostic cut-off values of the scoring scale based on the maximum Youden index were calculated according to the coordinates of each point on the ROC curve. The degree of calibration of the scoring scale was assessed using a consistency test (Kappa value).

Results

The average age was 68.28 ± 8.73 years, the gender ratio was 1:1.79, and the number of DR patients was 660 (34.8 %). The univariate analysis identified diabetes family history, treatment method, nephropathy, and duration, the smoking and alcohol habit, glycemic control, and the HbA1c level ($P < 0.05$) as DR associated factors. Gender, age, educational level, hypertension, hyperlipidemia, and diabetic foot were not associated ($P > 0.05$; Table 1).

The eight statistically significant factors identified in the univariate analysis were taken as independent variables in the multivariate logistic regression analysis (the forward LR method), which determined that the family diabetes history, the treatment method, diabetes duration, and glycosylated hemoglobin should be included in the final regression model.

After excluding other confounding factors (e.g., sex, age, education, hypertension, hyperlipidemia, diabetic nephropathy, diabetic foot, and BMI), the above factors in the final regression model were associated with and independent predictors of DR. Table 2 presents the partial regression coefficient (β), odds ratio (OR), and P-value for each factor. The statistical equation model (Equation 1) for predicting DR was:

$$P = -3.138 + 0.279X_1 + 0.730X_2 + 0.107X_3 + 0.244X_4$$

Equation 1: X_1 equals diabetes family history, X_2 equals the diabetes treatment method, X_3 equals the diabetes duration, and X_4 equals the HbA1c level.

The probability of suffering from DR per individual was calculated using the statistical equation model (Equation 2):

$$P = 1/[1 + e^{-(-3.138+0.279X_1+0.730X_2+0.107X_3+0.244X_4)}]$$

The complexity of the statistical equation models requires reliance on a calculator or computer, which limits the clinical applicability. Therefore, it was simplified to construct a simple scoring scale.

Based on the practical clinical significance, the diabetes duration was divided into four categories (<5, 5-9, 10-14, and ⩾15), and the HbA1c level was divided into three categories (<7.0, 7.0-9.9, ⩾10 %). Based on

the scoring system and the regression equation 2, a simple scoring scale for DR was constructed and had a maximum score of 12 points. Table 3 presents the score assignments of various risk factors.

The simple scoring scale was comprehensively evaluated by the ROC curve (Figure 1); the AUC was 0.753 (95 % confidence interval: 0.731-0.776). According to the coordinates of each point on the ROC curve, the diagnostic cut-off value at the maximum Youden Index was 3.5 points. According to the actual scoring, the cut-off value was 4 points. The sensitivity value was 0.665, the specificity value was 0.732, the positive predictive value was 0.570, the negative predictive value was 0.804, and the coincidence rate was 0.709 using a 4-point cut-off value. For early detection and to improve the sensitivity, a 3-point cut-off value was evaluated. The sensitivity value was 0.797, specificity value was 0.571, positive predictive value was 0.498, negative predictive value was 0.840, and the coincidence rate was 0.650.

Discussion

In this study, we combined several conventional clinical indicators to create a simple scoring scale for calculating DR risk in diabetes patients. The simplified scoring scale consisted of only the diabetes family history, treatment method, and duration, and the HbA1c level had a maximum

score of 12 points. The ROC curve demonstrated that the optimum cut-off for DR screening was 4 points, with 0.753 AUC, 0.665 sensitivity, and a 0.709 coincidence rate. Although the evaluation parameters of ROC were not ideal enough, for patients with complicated conditions, the scoring scale constructed in this study only complemented the clinical understanding and could not replace clinical evaluation and judgment. As a microvascular complication of progressive diabetes, the goal of the simple scale is to identify as many DR patients as early as possible. Therefore, to improve the sensitivity, the cut-off value was set to 3 points, which improved the sensitivity to 79.7 %. Practically, clinicians can quickly score patients using the 3- or 4-point cut-off to predict the possibility of DR in diabetes patients. The simplified scale can not only solve the prognosis prediction inaccuracy by a single index but also avoid the complexity of the prognosis statistical equation model. This allows doctors to quickly diagnose and provide treatment suggestions and gives patients an early warning. Therefore, implementing a new clinical prediction tool for screening DR needs time and clinical practice.

The univariate and multivariate logistic analyses showed that the HbA1c level was an independent high-risk factor for DR and played an important role in the overall scoring scale. The 2020 edition of the Chinese Guidelines for the Prevention and Treatment method of diabetes

stipulated that the individualized HbA1c level should be kept below 7 %.[22] Therefore, in this study, an HbA1c level of <7 % was used as the reference standard, which was assigned as 0 points on the scoring scale; 7 to 9.9 % was considered generally under control and received 1 point, and ⩾10 % was under poor control and received 3 points. The worse the glycemic control, the higher the HbA1c level and the greater the risk of DR in diabetes patients, which was consistent with the results of many studies in China and abroad. In two clinical trials, the United Kingdom Prospective Diabetes Study and the Diabetes Control and Complications Trial reported that the strict glycemic control (i.e., HbA1c, 7 %) decreased the DR incidence rate in type 1 and 2 DM.[23-24] Further, the risk of retinopathy was reduced by 30 to 40 % for every percent that the HbA1c level was lowered (e.g., from 8 to 7 %); the effect was called metabolic memory.[24-25] Recently, two cross-sectional studies from China also showed that the HbA1c level was an independent risk factor for DR, with ORs of 1.237 and 1.66, respectively. Thus, stringent glucose control is very important to reduce the occurrence and progression of DR.[26-27]

The diabetes duration was also an important DR risk factor. A retrospective cohort analysis from an academic outpatient department of endocrinology and metabolic diseases in Germany analyzed 17 461 consultations of 4513 patients with DM between 1987 and 2014. This

study demonstrated that the retinopathy prevalence increased depending on diabetes duration, starting at 1.1 % at diagnosis and ending at 63 % after 30 years or more.[28] Based on our study, the disease duration was divided into <5, 5-9, 10-14, ⩾15 years. According to the German results, the DR prevalence was lower if the patient's diabetes duration was less than five years. Therefore, diabetes diagnosed for <5 years was the reference group, and the DR risk score increased by 1 point for each additional five years. The maximum score was 12 points, and the highest score awarded based on the diabetes duration was 5 points, indicating that the diabetes duration was crucial for DR occurrence.

DM family history was an independent predictor of DR and increased the risk by 1.322 times. A genome-wide association meta-analysis assessed genes exhibiting the largest difference in glucose response for their association with DR.[29] The results showed that expression quantitative trait loci (eQTLs) of the glucose response genes were tested for DR associations. Another study detected an enrichment of the eQTLs from the glucose response genes among small association P-values and identified folliculin as a susceptibility gene for diabetic retinopathy.[30] Insulin, as a treatment for diabetes, also played an important role in the simple scale of this study. Although the mechanism of insulin affecting DR remains unclear, there are three possibilities. First, insulin-dependent

diabetes mellitus is more prone to microvascular and nervous system complications.[31] Second, a rapid improvement of blood glucose in diabetes patients due to insulin use caused the early worsening of diabetic retinopathy.[32] Third, an acute abundance of (exogenously administered) insulin enhanced ischemia-induced vascular endothelial growth factor expression, worsening DR.[33]

For a new clinical screening tool, it still needs time and clinical practice to test whether it can serve clinical medical staff and patients better. In the real world, clinicians in the endocrinology department can score patients with diabetes using a pre-prepared paper scoring scale during interrogation. Once the patient's score exceeds the threshold, the patient should be advised to switch to ophthalmology for diagnosis of DR. At the same time, for individual special patients with diabetes, the scoring scale constructed in this study should be used as a supplement to the clinical understanding, rather than a substitute for clinical evaluation and judgment. The present study has several limitations. First, although 93 % of patients with diabetes in China were over 50 years old, only individuals over 50 were included in this study because of the field investigation response rate. Thus, extrapolating the results should be done with caution. Second, the value of some predicted variables was a cross-sectional measurement, which observes a point value during the

patient investigation, and the timing sequence of outcomes and exposure could not be determined. Finally, only patients with diabetes from a single area were recruited for this study. Therefore, the conclusions of this study may have some limitations in extrapolation due to regional and ethnic oneness. Since we did not conduct external validation in other regions, it was difficult to extrapolate the results to all regions of China. In the future, further studies concerning other regions and ethnic groups in China are needed to verify our results.

Conclusions

In this study, diabetic patients were randomly selected from the local chronic disease management system to comprise the investigation population. Thus, a group case-control study was designed to screen for DR risk factors and construct a simplified predictive scale for identifying DR. The research subjects were well-represented, and the constructed scale had good effectiveness and accuracy. Therefore, we recommend that general practitioners use our simplified predictive scale for the quick and non-invasive early detection of DR.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee of the Affiliated Hospital of Nantong University (Approval No. 2019071). All participants provided written informed consent before data collection.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated during and analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Author contributions

Qiwei Ge and Min Li contributed equally to this work. Qiwei Ge and Min Li had full access to all of the data in study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Qiwei Ge, Min Li, Rongrong Zhu, Xun Zhuang

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Tables

Table 1. Univariate analysis of diabetic retinopathy related factors

Variable	DR (-) (n=1236)	DR (+) (n=660)	χ^2/t	P
Sex				
male	460(67.6)	220(32.4)	2.821	0.093
female	776(63.8)	440(36.2)		
Age				
50~	229(69.2)	102(30.8)		
60~	439(62.7)	261(37.3)	4.304	0.116
70~	568(65.7)	297(34.3)		
Education				
Illiteracy	584(63.8)	332(36.2)		
Primary school	381(67.6)	183(32.4)	2.840	0.417
Junior high school	204(66.2)	104(33.8)		
Senior high school	67(62.0)	41(38.0)		
Family history of diabetes				
No	1050(67.5)	506(32.5)	20.067	<0.001
Yes	186(54.7)	154(45.3)		
Treatment method of diabetes				
Diet control and exercise	477(87.7)	67(12.3)	231.801	<0.001
Oral medicine only	660(61.3)	417(38.7)		
Insulin	99(36.0)	176(64.0)		
Hypertension				
No	822(65.7)	430(34.3)	0.079	0.778
Yes	414(64.3)	230(35.7)		
Hyperlipidemia				
No	822(65.7)	430(34.3)	0.351	0.553
Yes	414(64.3)	230(35.7)		
Diabetic nephropathy				
No	1146(66.1)	588(33.9)	7.245	0.007
Yes	90(55.6)	72(44.4)		
Diabetic foot				
No	1196(65.2)	637(34.8)	0.083	0.774
Yes	40(63.5)	23(36.5)		
Smoking				
No/Quit	937(63.5)	539(36.5)	8.561	0.003

Yes	299(71.2)	121(28.8)		
Drinking alcohol				
No/Quit	990(63.3)	574(36.7)	14.069	<0.001
Yes	246(74.1)	86(25.9)		
glycemic control level				
<6.1	71(75.5)	23(24.5)		
6.1~	584(76.5)	179(23.5)	87.097	<0.001
⩾8.1	581(55.9)	458(44.1)		
Duration of diabetes(year)				
<5	619(86.8)	94(13.2)		
5-	398(67.7)	190(32.3)	361.013	<0.001
10-	124(35.0)	230(65.0)		
⩾15	95(39.4)	146(60.6)		
BMI (kg/m^2)				
<24	280(62.5)	168(37.5)	1.870	0.171
⩾24	956(66.0)	492(34.0)		
HbA1c (%)				
<7.0	603(76.3)	187(23.7)		
7.0-	466(61.0)	298(39.0)	88.457	<0.001
⩾10	167(48.8)	175(51.2)		

Table 2. Multivariate analysis of diabetic retinopathy related factors

Variable	β	SE	Wald	Sig	OR	95%CI
Constant term	-3.138	0.191	268.672	<0.001	-	-
Family history of diabetes	0.279	0.136	4.185	0.041	1.322	1.012-1.727
Treatment method of diabetes	0.730	0.103	50.451	<0.001	2.074	1.696-2.537
Duration of diabetes (year)	0.107	0.011	90.912	<0.001	1.113	1.089-1.138
HbA1c (%)	0.244	0.076	10.190	0.001	1.276	1.099-1.482

Table 3. The diabetic retinopathy score risk factors

Variable	β_i	Categories	Reference Value (W_{ij})	$\beta_i(W_{ij} - W_{iREF})$	SCORE $\beta_i(W_{ij} - W_{iREF})/B$
Family history of diabetes	0.279	0	0	0	0
		1	1	0.279	1
Treatment method of diabetes	0.730	0	0	0	0
		1	1	0.730	1
		2	2	1.460	3
HbA1c (%)	0.244	<7.0	4.95	0	0
		7.0~9.9	8.45	0.854	1
		⩾10	12.50	1.842	3
Duration of diabetes (year)	0.107	<5	2.5	0	0
		5-9	7.0	0.482	1
		10~14	12.5	1.070	2
		⩾15	27.5	2.675	5

calculation notes: Classify the risk factors and determine the reference value of each category as:

$C(i = 1,...,n;j = 1,...,C_i$; C_i is the total number of categories of risk factors).

Based on the original data distribution, the lower limit of hemoglobinA1c (HbA1c; %) was 3, the upper limit was 15, the lower limit of the diabetes duration was 1, and the upper limit was 40.

W_{iREF}: One category for each risk is a reference and assigned 0 points, recorded as: $W_{iREF}(i = 1,...,n)$. The HbA1c reference was <7.0 % and the diabetes duration reference was <5 years.

$\beta_i(W_{ij} - W_{iREF})$: Calculate the difference between the reference value of each category and the reference value of the reference category and multiply it by the corresponding weight coefficient of each risk factor, recorded as: $\beta_i(W_{ij} - W_{iREF})$, $(i = 1,...,n;j = 1,...,C_i$; C_i

is the total number of categories of risk factors).

B: Set a constant for the rating scheme system (i.e., determine a constant that makes the number of regression units for a certain category be assigned to 1 point, accordingly). In this study, the β coefficient of 5-times the age was taken as a fixed constant: $B = 5_{(0.107)} = 0.535$.

$\beta_i(W_{ij} - W_{iREF})/B$: Determine the score with each category per risk factor: $Scores_{ij}$

$(i = 1,\ldots,n; j = 1,\ldots,C_i$; C_i is the total number of categories of risk factors).

The relevant scores per risk factor in each category are calculated by: $Scores_{ij} = \beta_i(W_{ij} - W_{iREF})/B)$. The final score is the result rounded to the nearest integer value.

Table 4. The scale discrimination results

Scale Score	Clinical Diagnosis (Golden Standard)		Total
	DR (+)	DR (-)	
⩾4	439(66.5%)	331(26.8%)	770(40.6%)
<4	221(33.5%)	905(73.2%)	1126(59.4%)
Total	660(100.0%)	1236(100.0%)	1896(100.0%)

Figures

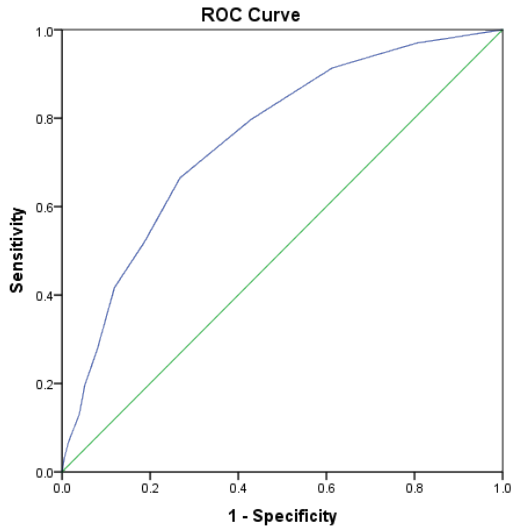

Figure 1. The simple scoring scale receiver operating characteristic (ROC) curve.

Figures

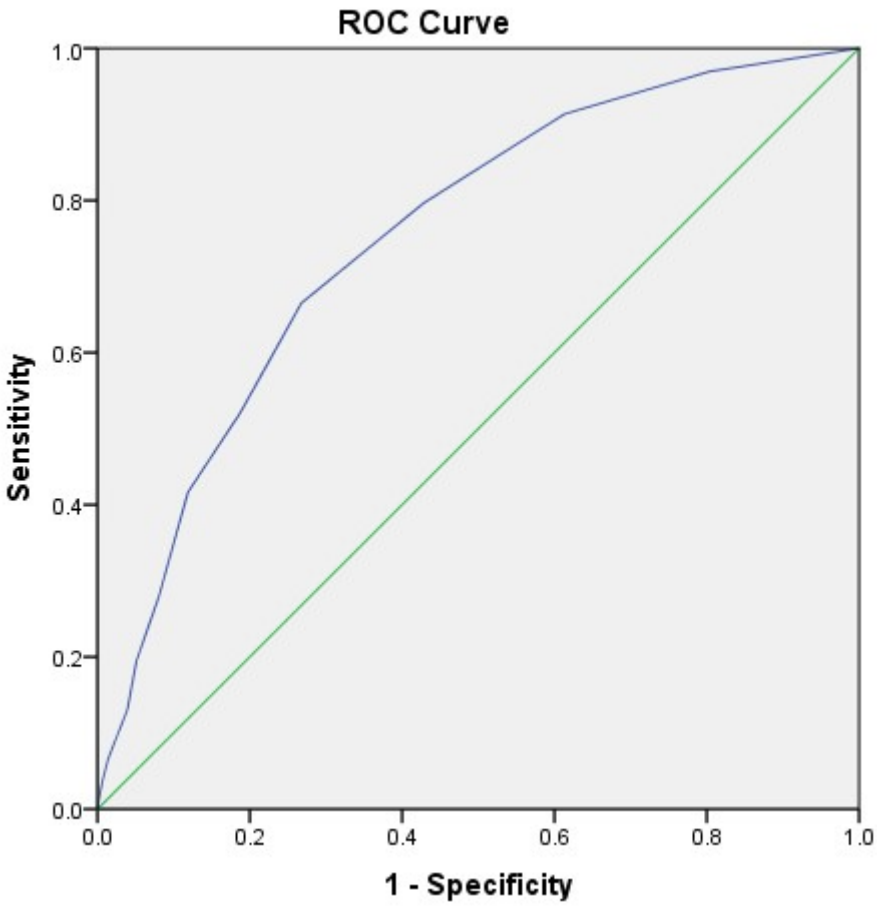

Figure 1

Supplementary Files

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- Tables.docx
- coveringletter.doc