· Original article ·

Nomogram including serum ferritin to predict the occurrence of diabetic retinopathy

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Foundation item：Quanzhou Medical and Health Field Guiding Science and Technology Project (No.2021N169S)

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Received：2023-05-07　　Accepted：2024-02-04

纳入血清铁蛋白的列线图预测糖尿病视网膜病变发生

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基金项目：泉州市医疗卫生领域指导性科技计划项目(No.2021N169S)

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摘要

目的：建立纳入血清铁蛋白的列线图模型预测糖尿病视网膜病变的发生,并评估该模型。

方法：通过单因素和多因素回归分析,筛选出包括铁蛋白在内的21个变量,确定了糖尿病视网膜病变的危险因素。建立列线图预测模型进行评估和校准。

结果：列线图模型纳入了铁蛋白、糖尿病病程、血红蛋白、尿微量白蛋白、用药规律性以及体重指数等6个变量。纳入血清铁蛋白的预测模型一致性指数为0.813(95%CI：0.748-0.879)。内外部验证的校准曲线表现良好,决策曲线提示阈值概率范围在10%-90%之间,该模型具有较高的净收益值。

结论：血清铁蛋白是糖尿病视网膜病变发生的重要危险因素。一种新的列线图模型,包括体重指数、糖尿病病程、铁蛋白、血红蛋白、尿微量白蛋白、用药规律性,具有较高的预测准确性,可为临床医生提供早期预判。

关键词：血清铁蛋白;糖尿病视网膜病变;列线图;预测

Abstract

• AIM：To establish a nomogram model to predict the effect of serum ferritin on diabetic retinopathy and evaluate the model.

• METHODS：A total of 21 variables，including ferritin，were screened by univariate and multivariate regression analysis to determine the risk factors of diabetic retinopathy. A nomogram prediction model was established for evaluation and calibration.

• RESULTS：Ferritin，duration of diabetes，hemoglobin，urine microalbumin，regularity of medication and body mass index were included in the nomogram model. The consistency index of the prediction model with serum ferritin was 0.813（95% CI：0.748-0.879）. The calibration curves of internal and external verification showed good performance，and the probability of the threshold suggested by the decision curve was in the range 10% to 90%. The model had a high net profit value.

• CONCLUSIONS：Serum ferritin is an important risk factor for diabetic retinopathy. A new nomogram model，which includes body mass index，duration of diabetes，ferritin，hemoglobin，urine microalbumin and regularity of medication，has a high predictive accuracy and could provide early prediction for clinicians.

• KEYWORDS：serum ferritin; diabetic retinopathy; nomogram; prediction

Citation：Wu XY, Xie DD, Chen JN, et al. Nomogram including serum ferritin to predict the occurrence of diabetic retinopathy. Guoji Yanke Zazhi(Int Eye Sci)，2024,24(5)：671-676.

INTRODUCTION

The pathogenesis of diabetic retinopathy is complex and diverse. Morphologically，it is caused by ischemic changes in retinal microvessels induced by high sugar，which leads to cell proliferation，glial degeneration，and neovascularization. At the molecular level，pathogenesis includes oxidative stress，chronic inflammation[1]，apoptosis and autophagy. Recently，iron-dependent regulatory cell death has become a hot topic. Serum iron is involved in a variety of metabolic pathways，and ferric and bivalent ions are converted by redox reactions，while unstable iron pools often induce lipid peroxidation and trigger ferroptosis. Studies have found that the body controls the abundance of iron pools by regulating the level of the iron storage protein ferritin，which，in turn，triggers or inhibits ferroptosis[2]. This paper aimed to

establish a nomogram model to evaluate the predictive effect of serum ferritin on diabetic retinopathy.

SUBJECTS AND METHODS

The study was conducted retrospectively in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the 910th Hospital with the ethical approval number 2021 (No.46). All subjects gave informed consent to participate and signed the consent form, which is in accordance with the TRIPOD statement.

Patients who received ophthalmic consultation from the Department of Endocrinology in the 910th Hospital of Joint Services Support Force from 2018 to 2021 and met the diagnostic criteria for diabetes established by the World Health Organization in 1998 were enrolled[3]. Measurement of serum ferritin was performed routinely in all patients in our institute. The admission criteria were as follows: 1) a complete medical history; 2) voluntary enrollment and not lost to follow-up; 3) ferritin, hemoglobin, serum creatinine (Scr), urine microalbumin (UMA), blood lipids, glycosylated hemoglobin (HbA1c), and fasting blood glucose were tested at admission; 4) the same ophthalmologist checked the retina to determine whether diabetic retinopathy was present, and the result was clear. Exclusion criteria were as follows: 1) unable to provide an accurate and effective medical history; 2) the inspection results were incomplete; 3) lost to follow-up; 4) a history of ophthalmic surgery or treatment, and the retina examination was not clear.

Data Collection Clinical data of patients consisted of the patients' oral account and hospital inpatient case data. Risk variables were determined based on guidance from the literature combined with the actual situation in our hospital[4]. The variables included sex, age, body mass index (BMI), type of diabetes, family history, duration of diabetes, type of medication, regularity of medication, cigarette smoking, alcohol drinking, hypertension, HbA1c, high-density lipoprotein, low-density lipoprotein, total cholesterol, triglycerides, fasting blood glucose, ferritin, hemoglobin, Scr, and UMA. Two members of the research group checked the hospitalization records and confirmed the information with the relevant subjects. The duration of diabetes was defined as the time from the initial diagnosis of diabetes to the date of data collection. The type of medication was classified as whether insulin was frequently used by subcutaneous injection during treatment. Regularity of medication was defined as whether there was any prolonged drug withdrawal or self-adjustment of more than 3 days during treatment in the preceding 6 mo. Smoking referred to smoking ≥0.5 of a pack per day after the diagnosis of diabetes, and drinking referred to drinking ≥250 mL per week after the diagnosis of diabetes. The third member of the research group entered the data into the system for statistical analysis. Diabetic retinopathy was graded according to international clinical grading standards[5]. The same physician determined the grouping of subjects according to the results of retinal examinations (fundus microscopy or fundus fluorescence angiography) into a group without diabetic retinopathy and a group with diabetic retinopathy.

Statistical Analysis The 21 variables comprised 13 with measurement data and 8 with counting data. Measurement data consistent with normal distribution were represented by mean standard deviation. Independent sample t-tests were used for comparison between groups, measurement data inconsistent with normal distribution was represented by $[M(P_{25}, P_{75})]$, and the Mann-Whitney U test was used for comparisons between groups. Counting data were expressed as cases and percentages, and the Chi-square test was used for comparisons between groups. Unclassified logistic univariate regression analysis was used for both measurement and counting data, and $P \leq 0.15$ was regarded as a statistically significant difference with consistent results. Variables with statistical differences and non-common variables in univariate analysis were included in multivariate logistic regression analysis to generate a forest plot. Independent factors from the regression results were used as predictors to establish a nomogram model. The training set and validation set were randomly divided 3:1 to calculate the consistency index of the model. The area under the curve was calculated using the receiver operating characteristic (ROC) curve, the calibration curve was used to evaluate the accuracy of the model, and decision curve analysis was used to evaluate the clinical benefit rate.

RESULTS

From 2018 to 2021, a total of 631 patients with diabetes underwent ophthalmic consultation. Of the 453 patients (after excluding the purpose of consultation as being inconsistent and repeated cases from 631 subjects), a total of 327 cases were finally included in the study after screening according to the inclusion and exclusion criteria. There were 256 cases in the group without diabetic retinopathy and 71 cases in the group with diabetic retinopathy. Single logistic regression analysis showed that sex, type of diabetes, cigarette smoking, high-density lipoprotein, low-density lipoprotein, total cholesterol and triglycerides had little effect on the occurrence of diabetic retinopathy ($P \geq 0.15$). This finding was consistent with the lack of significant differences between the two groups (independent sample t-tests or Chi-square test). By contrast, effects on the occurrence of diabetic retinopathy were found in the univariate logistic analysis ($P < 0.15$) for age, BMI, family history, type of medication, regularity of medication, duration of diabetes, alcohol drinking, hypertension, HbA1c, fasting blood glucose, ferritin, hemoglobin, Scr, and UMA. This finding was also consistent with the statistical differences between the two groups (independent sample t-tests or Chi-square tests, or Mann-Whitney U tests, Table 1).

Combined with the results of univariate logistic regression analysis and comparison between the two groups (independent sample t-tests, Chi-square tests and Mann-Whitney U tests), a total of 14 variables including 9 continuous variables and 5 dichotomy variables were included in the multivariate

Table 1　Characteristics of the two groups

Variables	NDR ($n=256$)	DR ($n=71$)	$T/X^2/U$ P	Univariate analysis OR (95% CI)	P
Age ($\bar{x}\pm s$, y)	52.73±12.45	55.21±10.02	0.084[a]	1.018 (0.995, 1.041)	0.124[a]
BMI [M (P_{25}, P_{75}), kg/m²]	23.92 (22.21, 26.64)	23.14 (21.05, 24.61)	0.006[a]	0.892 (0.823, 0.967)	0.005[a]
Sex			0.832	1.062 (0.610, 1.849)	0.832
Female (n, %)	90 (35.2)	24 (33.8)			
Male (n, %)	166 (64.8)	47 (66.2)			
Type			0.252	3.143 (0.399, 24.764)	0.277
T1D (n, %)	11 (4.3)	1 (1.4)			
T2D (n, %)	245 (95.7)	70 (98.6)			
Family History			0.102[a]	1.682 (0.899, 3.150)	0.104[a]
No (n, %)	213 (83.2)	53 (74.6)			
Yes (n, %)	43 (16.8)	18 (25.4)			
Type of medication			0.024[a]	1.843 (1.079, 3.147)	0.025[a]
No insulin (n, %)	174 (68.0)	38 (53.5)			
Insulin (n, %)	82 (32.0)	33 (46.5)			
Regularity of medication			0.001[a]	0.402 (0.230, 0.704)	0.001[a]
No (n, %)	121 (47.3)	49 (69.0)			
Yes (n, %)	135 (52.7)	22 (31.0)			
Duration of diabetes [M (P_{25}, P_{75}), a]	4.0 (1.0, 9.0)	10.0 (3.0, 14.0)	0.000[a]	1.115 (1.065, 1.167)	0.000[a]
Cigarette smoking			0.233	0.629 (0.292, 1.354)	0.236
No (n, %)	208 (81.3)	62 (87.3)			
Yes (n, %)	48 (18.8)	9 (12.7)			
Alcohol drinking			0.140[a]	1.772 (0.822, 3.820)	0.144[a]
No (n, %)	232 (90.6)	60 (84.5)			
Yes (n, %)	24 (9.4)	11 (15.5)			
Hypertension			0.035[a]	1.763 (1.037, 2.998)	0.036[a]
No (n, %)	165 (64.5)	36 (50.7)			
Yes (n, %)	91 (35.5)	35 (49.3)			
HbA1c [M(P_{25}, P_{75}), %]	8.75 (7.00, 11.10)	9.70 (8.30, 12.20)	0.002[a]	1.146 (1.038, 1.264)	0.007[a]
HDL ($\bar{x}\pm s$, mmol/L)	1.23±0.34	1.23±0.33	0.948	1.026 (0.470, 2.241)	0.948
LDL ($\bar{x}\pm s$, mmol/L)	2.92±1.07	3.00±1.02	0.557	1.077 (0.842, 1.376)	0.556
TC ($\bar{x}\pm s$, mmol/L)	4.89±1.37	4.94±1.31	0.791	1.027 (0.847, 1.245)	0.790
TG ($\bar{x}\pm s$, mmol/L)	2.13±1.97	2.12±2.08	0.958	0.996 (0.872, 1.138)	0.958
Fasting blood glucose ($\bar{x}\pm s$, mmol/L)	9.95±5.27	11.28±6.52	0.076[a]	1.038 (0.995, 1.084)	0.084[a]
Ferritin ($\bar{x}\pm s$, ng/mL)	377.81±324.48	498.92±443.73	0.035[a]	1.001 (1.000, 1.002)	0.014[a]
Hemoglobin [M (P_{25}, P_{75}), g/L]	142.00 (128.00, 153.00)	130.00 (109.00, 143.00)	0.000[a]	0.973 (0.961, 0.986)	0.000[a]
Scr [M (P_{25}, P_{75}), umol/L]	62.20 (51.60, 78.30)	76.70 (57.00, 110.30)	0.000[a]	1.007 (1.003, 1.012)	0.001[a]
UMA [M(P_{25}, P_{75}), mg/L]	12.15 (10.50, 40.80)	44.90 (11.60, 507.00)	0.000[a]	1.001 (1.000, 1.002)	0.000[a]

NDR：No diabetic retinopathy；DR：Diabetic retinopathy；BMI：Body mass index；T1D：Type 1 diabetes；T2D：Type 2 diabetes；HbA1c：Glycosylated hemoglobin A1c；HDL：High-density lipoprotein；LDL：Low-density lipoprotein；TC：Total cholesterol；TG：Triglyceride；Scr：Serum creatinine；UMA：Urine microalbumin. [a]$P<0.15$.

logistic regression analysis. The Hosmer-Lemeshow test result was $P=0.126>0.05$, which indicated that the model had a good fit. The percentage correction was 82.9%, indicating high accuracy of the model. Figure 1 shows the odds ratios, P-values and corresponding forest plot for each variable after multivariate analysis. Six variables, BMI, duration of diabetes, ferritin, hemoglobin, UMA and regularity of medication, were independent factors for the occurrence of diabetic retinopathy ($P<0.05$). The odds ratio values of ferritin, hemoglobin, and UMA were not high and their influence on the occurrence of diabetic retinopathy was low,

which may be the result of the small sample size in our study. However, according to the clinical experience and statistical results, we believe that these three test variables contribute meaningfully to the occurrence of diabetic retinopathy, so they were included in the nomogram analysis. Using R software and loading the R package, 327 cases of data were divided into a training set of 246 cases and a validation set of 81 cases in a ratio of 3：1. The 6 variables, BMI, duration of diabetes, ferritin, hemoglobin, UMA and regularity of medication were used to establish a nomogram model, as shown in Figure 2. Among them, BMI, hemoglobin and regularity of medication

were protective factors, whereas ferritin, UMA and duration of diabetes were risk factors. For example, for an individual with a BMI of 24 kg/m^2 (60 points), ferritin 500 ng/mL (12 points), a duration of diabetes of 20 years (40 points), hemoglobin 90 g/L (47 points), UMA 500 mg/L (10 points) and irregular medication (21 points), the total score would be 190 points, which corresponds to an incidence of diabetic retinopathy of 0.86.

The goodness-of-fit test results of the model showed that the consistency index was 0.813 (95% CI: 0.748 - 0.879), whereas the area under the ROC curve obtained by the validation set was 0.809 (95% CI: 0.656-0.962), indicating good discrimination. The calibration graph in the training set showed a good prediction accuracy close to the ideal curve through the internal verification re-sampling technique (Bootstrap), while the calibration graph curve of the external verification (cross verification technique) was also evenly distributed near the ideal curve, indicating high accuracy of the model. The decision curve analysis indicated that the model had a higher net profit value in the range of 10%-90% threshold probability (Figure 3).

DISCUSSION

Diabetic retinopathy is a common complication of diabetes with a high prevalence[6-7], which can lead to blindness in severe cases. Early screening, diagnosis, and treatment are effective preventive measures for diabetic retinopathy. A nomogram is a simple, convenient and personalized method to predict the occurrence of disease by visualizing a graph[8]. Chinese researchers have previously used a nomogram to predict the occurrence of diabetic retinopathy[9]. The nomogram contained ocular axis, duration of diabetes, age, HbA1c and albuminuria, which indicates that this model is highly feasible. Subsequently, based on community data, a diabetic retinopathy risk prediction model was built[10], which included duration of diabetes, systolic blood pressure, fasting blood glucose, HbA1c, and low-density lipoprotein cholesterol. This model also obtained high predictive values. Most researchers have concluded that age, duration of diabetes, fasting blood glucose and HbA1c are influencing factors. Additionally, blood pressure, heart rate, triglycerides[4], smoking[11] and BMI[12] are possible influencing factors. Some researchers believe that retinol-binding protein 4, neutrophil-lymphocyte ratio and platelet-lymphocyte ratio may also be involved in the occurrence and development of diabetic retinopathy[13]. Measurement of adiponutrin and pannexin 1, which have regulatory roles in hyperglycemia and insulin resistance, may aid clinicians in determining the risk of diabetic retinopathy development[14]. A meta-analysis showed that the elevated cystatin C is closely related with diabetic retinopathy and probably plays a critical role in its progression[15]. The liver factor ectodysplasin A, which causes a disorder of body fat metabolism by affecting insulin sensitivity, also has a significant impact in a constructed diabetic retinopathy prediction model[16].

Serum ferritin is a cage macromolecular protein with an inner diameter of 8 nm and an outer diameter of 12 nm assembled by 24 subunits of heavy and light chains[17]. It has hydrophilic and hydrophobic channels on its surface and can store up to
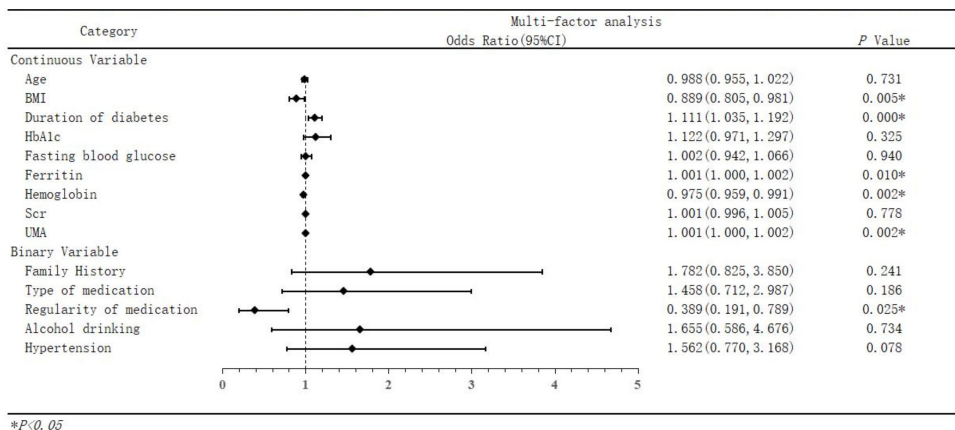

Category	Multi-factor analysis Odds Ratio(95%CI)		P Value
Continuous Variable			
Age		0.988(0.955,1.022)	0.731
BMI		0.889(0.805,0.981)	0.005*
Duration of diabetes		1.111(1.035,1.192)	0.000*
HbA1c		1.122(0.971,1.297)	0.325
Fasting blood glucose		1.002(0.942,1.066)	0.940
Ferritin		1.001(1.000,1.002)	0.010*
Hemoglobin		0.975(0.959,0.991)	0.002*
Scr		1.001(0.996,1.005)	0.778
UMA		1.001(1.000,1.002)	0.002*
Binary Variable			
Family History		1.782(0.825,3.850)	0.241
Type of medication		1.458(0.712,2.987)	0.186
Regularity of medication		0.389(0.191,0.789)	0.025*
Alcohol drinking		1.655(0.586,4.676)	0.734
Hypertension		1.562(0.770,3.168)	0.078

*P<0.05

Figure 1 Multivariate logistic regression analysis to identify risk factors of diabetic retinopathy with the Forest plot.
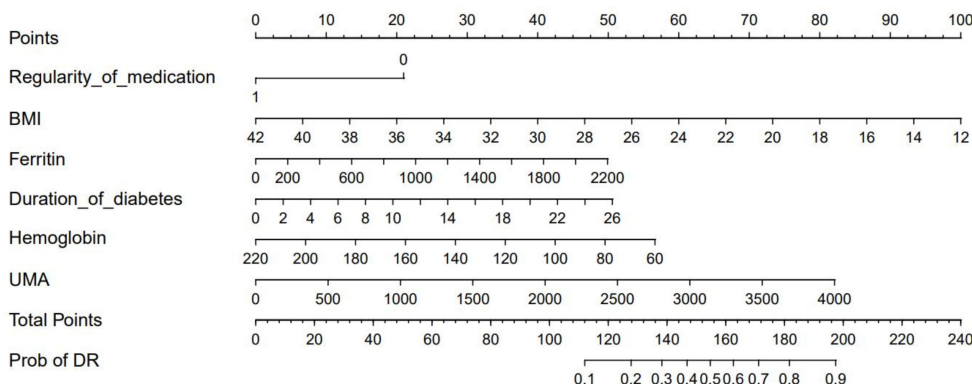

Figure 2 A nomogram including serum ferritin to predict the occurrence of diabetic retinopathy.
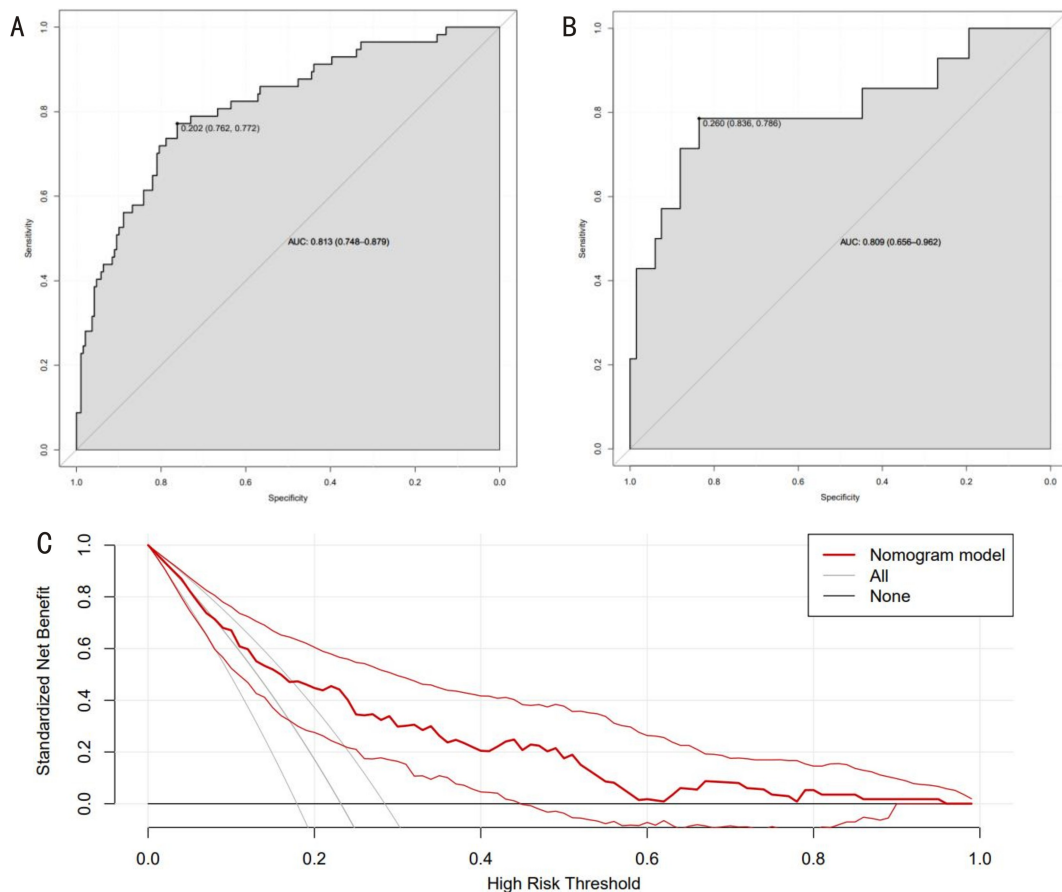
Figure 3　Evaluation and calibration of the nomogram prediction model.　A：Receiver operating characteristic curve of the training set；B：Receiver operating characteristic curve of the validation set；C：Decision curve analysis of the training set.

4 500 iron atoms in the form of hydro iron minerals[18]. Its secondary structure is an α-helical structure with a functional domain of ferritin-like oxidation[19]. The serum ferritin level of patients with diabetic retinopathy is increased.

A study with 5 321 subjects investigated the relationship between serum iron and the occurrence of diabetic retinopathy and found that serum iron was negatively correlated with the occurrence of diabetic retinopathy[20]. This was achieved by exploring the serum iron threshold through the ROC curve. Another cross-sectional study found that hyperferritinemia was an independent risk factor for diabetic retinopathy[21]. In this study, ferritin was included as one of the factors affecting the incidence of diabetic retinopathy, and six factors including ferritin were eventually involved in the construction of a nomogram model. The results indicated that ferritin was an independent risk factor affecting the occurrence of diabetic retinopathy, which was consistent with a previous literature report[21].

The lower the BMI value in our model, the higher the integral value of diabetic retinopathy. This finding suggests that the thinner people are, the higher the risk of diabetic retinopathy. This finding differs from that of previous studies[12], and we believe that the reason may lie in the statistical method used. In the present study, BMI was not converted twice, and the continuous variables were directly used for statistics; therefore, the results may be closer to the real - world situation. A meta-analysis and systematic review provided an favorable evidence that neither being overweight nor obesity was associated with an increased risk of diabetic retinopathy[22], which is consistent with our view. Reduced hemoglobin was associated with increased risk of diabetic retinopathy in our study, which was related to the occurrence of diabetic nephropathy reported in another study[23]. Most researchers have recognized that the duration of diabetes and UMA are risk factors for the occurrence of diabetic retinopathy. The earlier the age of onset of diabetes, the higher the incidence of diabetic retinopathy[24]. Likewise, the greater the quantity of UMA[9], the higher the incidence of diabetic retinopathy. Regular medication is an effective means to prevent diabetes complications, and the incidence of diabetic retinopathy will also be reduced, which is verified by this model. At present, an online screening tool, which could help clinicians in conducting diabetic retinopathy risk assessments, is now available[25].

The pathogenesis of diabetic retinopathy involves vascular injury induced by various metabolic pathway disorders caused by hyperglycemia in the body. Pericellular apoptosis, up - regulation of vascular endothelial growth factor, and high expression of inflammatory factors are all direct evidence of blood vessel damage caused by hyperglycemia[26]. Recent studies have shown that retinal neurodegenerative changes occur earlier than microvascular lesions[27]. Ferroptosis is a kind of programmed cell death caused by the accumulation of lipid peroxides dependent on iron. Reducing the production of

reactive oxygen species can effectively improve visual acuity and reduce retinal optic nerve apoptosis[28]. Shao et al[29] studied a diabetic retinopathy rat model and verified ferroptosis and cell damage caused by increased oxidative stress, while ferrostatin 1 alleviated tissue and cell damage in this diabetic retinopathy model by improving the antioxidant capacity of the Cystine/glutamate Antiporter system XC− and glutathione peroxidase 4. Hou et al[30] showed that nuclear receptor coactivator 4 − mediated ferritin degradation is involved in ferroptosis. Chen et al[31] found that ataxia telangiectasia mutated inhibition rescued ferroptosis by increasing the expression of iron regulators involved in iron storage (ferritin heavy and light chain) and export (ferroportin, FPN1).

We explored the predictive effect of ferritin on the occurrence of diabetic retinopathy and found that serum ferritin is an important risk factor for diabetic retinopathy. This study provides real-world theoretical support for the in-depth study of ferroptosis in diabetic retinopathy. Furthermore, the nomogram model could help non − ophthalmic physicians to efficiently screen patients. However, the sample size was small, and the results have certain limitations; therefore, similar studies are warranted.

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