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Optical coherence tomography angiography in diabetic retinopathy: focusing on microvascular changes

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应用 OCTA 观察糖尿病视网膜病变的微血管变化

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摘要

目的:探究光学相干断层血管造影(OCTA)参数在糖尿病视网膜病变(DR)诊断中的价值,并为糖尿病肾病(DN)患者提供更灵敏的 OCTA 筛查参数,以便在疾病早期诊断 DR 的并发。

方法:纳入 2022/2023 就诊于中山大学附属第七医院眼科的患者 200 例,其中包括 95 例首次诊断为 DR 的患者和 105 例未诊断为 DR 的患者,所有患者均进行 OCTA 检查,收集人口统计数据和肾功能参数。经质量检查后,测量患者 3 mm×3 mm 和 6 mm×6 mm窗口的中央凹无血管区面积、血管密度(VD)和灌注密度(PD)指标情况。

结果:利用随机森林和多因素回归方法建立一个基于 12 个变量(年龄、血糖、血压、血脂、糖化血红蛋白、尿素、糖尿病持续时间、HUA、DN、CMT)的 DR 诊断模型。添加特定的 OCTA 参数(6 mm×6 mm 窗口中的外层血管密度,AUC=0.837 *vs* 0.819,$P=0.03$)增强了现有 DR 诊断模型的有效性。在对 DN 患者的研究中,6 mm×6 mm 窗口中的参数(内层血管密度;外层血管密度;全血管密度;外层灌注密度;全灌注密度)提高了 DR 的诊断效果。

结论:6 mm×6 mm 窗口中外层血管密度参数的加入可以提高传统 DR 诊断模型的效果。同时,与 3 mm×3 mm 窗口相比,聚焦于 6 mm×6 mm 窗口中的微血管参数对诊断 DN 患者并发 DR 更有意义。

关键词:光学相干断层血管造影(OCTA);糖尿病视网膜病变;糖尿病肾病;预测模型

Abstract

• AIM: To investigate the value of optical coherence tomography angiography (OCTA) indicators in the diagnosis of diabetic retinopathy (DR), and to provide patients with diabetic nephropathy (DN) with more sensitive OCTA screening indicators to detect concurrent DR at an early stage.

• METHODS: A total of 200 patients who treated in the ophthalmology department of the Seventh Affiliated Hospital, Sun Yat-sen University from 2022 to 2023 were included, including 95 first-diagnosed DR patients and 105 patients without DR, and all patients underwent OCTA examination and a collection of demographics and renal function parameters. After a quality check, automated measurements of the foveal avascular zone area, vessel

density (VD), and perfusion density (PD) of both 3 mm×3 mm and 6 mm×6 mm windows were obtained.

• RESULTS: Using random forest and multivariate Logistic regression methods, we developed a diagnostic model for DR based on 12 variables (age, FBG, SBP, DBP, HbA1c, ALT, ALP, urea/Scr, DM duration, HUA, DN, and CMT). Adding specific OCTA parameters enhanced the efficacy of the existing diagnostic model for DR (outer vessel density in 6 mm×6 mm window, AUC=0.837 *vs* 0.819, *P*=0.03). In the study of DN patients, the parameters in the 6 mm×6 mm window improved the diagnostic efficacy of DR (inner VD; outer VD; full VD; outer PD; full PD).

• CONCLUSION: The outer VD in the 6 mm×6 mm window can enhance the efficacy of the traditional DR diagnostic model. Meanwhile, compared with the 3 mm×3 mm window, the microvascular parameters in the 6 mm×6 mm window focusing on DN patients can be more sensitive to diagnosing the occurrence of DR.

• KEYWORDS: optical coherence tomography angiography (OCTA); diabetic retinopathy; diabetic nephropathy; prediction model
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INTRODUCTION

Diabetic retinopathy (DR) is the most common microvascular complication of diabetes mellitus (DM) and one of the leading causes of visual impairment and blindness in the world[1], which impairs visual function in 14.77% to 22.43% of diabetic patients in China[2]. Clinically feasible screening methods can play an essential role in improving DR diagnosis, especially in the early stage of DR. Whereas early identification and prediction of DR is a critical but burdensome step in DR management.

Currently, more and more researchers are working on building or improving existing predictive models for DR. Mo *et al*[3] and Yang *et al*[4] developed risk nomograms for predicting DR, showing that patient demographic characteristics and biochemical variables such as diabetic nephropathy (DN), diabetes duration, and blood pressure are risk factors for DR. However, they suggested that information such as optical coherence tomography (OCT) and optical coherence tomography angiography (OCTA) should be added to construct a diagnostic model. In recent years, OCTA has entered a new phase in visualizing retinal microvasculature. Compared with conventional fundus fluorescence angiography (FFA), OCTA has the advantages of being fast, noninvasive, and high-resolution, which not only reveals different capillary plexuses but also quantifies retinal hemodynamic parameters, such as the foveal avascular zone (FAZ), retinal vessel density (VD), and perfusion density (PD)[5-6]. Previous studies quantified retinal microvasculature in diabetic patients without clinical retinopathy and in patients with early DR, suggesting that OCTA parameters may be potential biomarkers of DR[7]. OCTA is available in scans of increasing size (3 mm×3 mm, 6 mm×6 mm, and 8 mm×8 mm), and the OCTA indexes vary with different measurement regions[8]. The smallest OCTA scans achieve the highest resolution, so previous studies investigating associations with DR focused on 3 mm ×3 mm OCTA images or just utilized one-sized OCTA scan[9]. In a prospective study, Sun *et al*[10] found that the FAZ area and VD of the deep capillary plexus (DCP) predicted the progression of DR. Similarly, Yuan *et al*[11] noted a similar role for information on the peripapillary microvasculature of the super capillary plexus (SCP). Nonetheless, they all used a small field of view (3 mm × 3 mm) in their OCTA scans and lacked assessment of the peripheral retina.

At the same time, we noted that most studies only explored the predictive value of OCTA metrics for the occurrence of DR without a comprehensive assessment in conjunction with systemic factors. Therefore, we established a diagnostic model for DR by collecting a series of demographic information and diabetes-related factors and further evaluated the OCTA indexes of different DR scanning regions based on the traditional model in order to explore whether these OCTA indexes can improve the predictive discriminatory ability of DR progression, identify the high-risk group of diabetic microvascular complications, and then help physicians to formulate the patient's individual screening and treatment planning.

The interrelationship between DR and DN is currently receiving much attention. Several studies have shown a close association between the occurrence and development of these two common diabetic microangiopathies. According to a large-scale epidemiological survey conducted by the Chinese Center for Disease Control and Prevention, the number of people with both diseases may exceed 2.5 million. Although they share a similar pathogenesis, the order of occurrence between the two diseases is unclear. Here, for patients with DN, we explored more sensitive OCTA indicators for predicting the progression of DR, providing new insights for early identification and treatment.

SUBJECTS AND METHODS

Ethical Approval The Department of Ophthalmology at the Seventh Affiliated Hospital of Sun Yat-sen University in Guangzhou, China, implemented the ongoing prospective observational study. The study complied with the principles of the Declaration of Helsinki and was approved by the Seventh Affiliated Hospital Ethics Committee of Sun Yat-sen University (No. KY-2021-083-01). All participants were informed and signed a written informed consent.

Subjects The research subject was chosen from 238 diabetic patients who visited the ophthalmology department of the Seventh Affiliated Hospital of Sun Yat-sen University from

2022 to 2023. Inclusion criteria were 1) age >18 years; 2) diagnosis of type 1 or type 2 diabetes. Exclusion criteria were 1) proliferative diabetic retinopathy (PDR) at baseline; 2) history of panretinal photocoagulation therapy or focused laser therapy within 6 mo prior to recruitment; 3) history of cataract surgery or other intraocular surgeries within 6 mo prior to recruitment; 4) ungradable OCTA images, structural OCT images, or color fundus photographs; 5) refractive media clouding that resulted in poor OCTA imaging quality, with a picture signal intensity of less than 6/10. Totally 95 patients were first diagnosed with nonproliferative diabetic retinopathy (NPDR) who had never received any relevant ophthalmic treatment, and 105 patients without DR were included in the study. The diagnosis of NPDR is based on both fundus photography and FFA. Among 200 patients, 45 of 77 diabetic peripheral vascular disease(DPA) patients had DR; 19 of 37 diabetic peripheral neuropathy(DPN) patients had DR; 25 of 32 DN patients had DR; 30 of 43 hyperuricemia (HUA) patients had DR; 23 of 45 atherosclerosis(AS) patients had DR; 28 of 68 hyperlipidemia(HPL) patients had DR; all 5 diabetic macular edema(DME) patients had DR; and 5 of 8 ocular media opacity(OMO) patients had DR.

Demographic and Clinical Data Collection Age was defined as the period between birth and the examination. The duration of DM and high blood pressure (HBP) was defined as the interval between the test and the date of the first diagnosis. Blood pressure, including systolic blood pressure (SBP) and diastolic blood pressure (DBP), was measured based on the average of twice - repeated measurements according to the protocol of Hypertension Detection. The glycosylated hemoglobin (HbA1c) and fasting blood glucose (FBG), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), urinary albumin (Urea), serum creatinine (Scr), were obtained from the results of the blood biochemistry test and routine blood test at the examination. Central macular thickness (CMT) was acquired from the OCT results operated by an experienced doctor at the examination. The patient's disease information, including DME, OMO, DN, DPA, DPN, HUA, AS, and HPL, was obtained from records. DN can be diagnosed when the urinary albumin/creatinine ratio (UACR) of diabetes patients exceeds 30 mg/g at least twice in 3 to 6 mo, or the estimated glomerular filtration rate (eGFR) continues to be lower than 60 mL/min/1.73 m^2 for more than 3 mo, and after excluding infection and other possible interference factors.

Optical Coherence Tomography Angiography Imaging and Measurements All subjects were imaged with the Zeiss Cirrus HD-5000 Spectral-Domain OCT with AngioPlex OCT Angiography (Carl Zeiss Meditec, Dublin, CA) that has a scan rate of 68000 A-scans per second, central wavelength of 840 nm, motion tracking to reduce motion artifact and uses an optical microangiography (OMAG) algorithm for analysis. Both 3 mm ×3 mm and 6 mm ×6 mm images centered on the fovea were acquired. The poor scanning quality of OCTA images caused by low resolution or low saturation and the motion artifacts because of poor collaboration were excluded. The software (Carl Zeiss Meditec version 10.00.14618) automatically detects the inner and outer boundaries of the SCP slab. The software quantified the average VD and PD using a grid overlay according to the standard ETDRS subfields. VD was defined as the total length of perfused retinal microvasculature per unit area in the measurement region. In contrast, PD was defined as the total area of perfused retinal microvasculature per unit area in a part of the measurement. VD and PD were calculated for the 3 mm circle and 3 mm ring for 3 mm×3mm images and over the entire ETDRS 6 mm circle for 6 mm×6 mm scans (Figure 1). The software automatically calculated FAZ boundaries; values with inaccurate boundaries identified on manual review were excluded.

Statistical Analysis All statistical analyses were performed with R (R Foundation for Statistical Computing, Vienna, Austria) version 4.2.1. Categorical variables are described as numbers and percentages. Continuous variables following normal distribution are described as mean ± SD. The Kolmogorov-Smirnov test was applied for normal distribution. The difference in parameters at baseline among groups was compared using a t-test or χ^2 test. The random forest (RF) was used to select the variables for establishing the model, and then the diagnostic model of DR was established using Logistic regression (LR). Then, OCTA measurement variables were added to the diagnostic model one by one to find variables that could sensitively predict DR diagnosis. Model performance was measured using the concordance index, calibration plots, and Brier score. In addition, receiver operating characteristic (ROC) curve and integrated discrimination improvement (IDI) analyses were performed to examine the incremental usefulness of adding OCTA measures to the prediction of first diagnosed DR. Decision curve analyses were performed to obtain a value of the net benefit of using the model at that threshold. The associations were quantified using P value, relative risk (RR), and 95% confidence interval (95% CI). $P<0.05$ was considered statistically significant.

RESULTS

A total of 200 DM patients had OCTA imaging at the baseline examination. Table 1 summarizes the features of 95 patients first diagnosed as NPDR who had never received any related ophthalmological treatment and 105 patients without DR. For the DR group ($n=95$), HbA1c (9.9±2.5 *vs* 9.0±2.4, $P=0.012$) and age (53.1±10.2 *vs* 46.6±10.1, $P<0.001$) was statistically significantly higher than the group without DR. Meanwhile, both DM and HBP duration are longer in DR patients.

Filtering of Diagnostic Model Variables We select modeling indicators from biochemical indicators and other

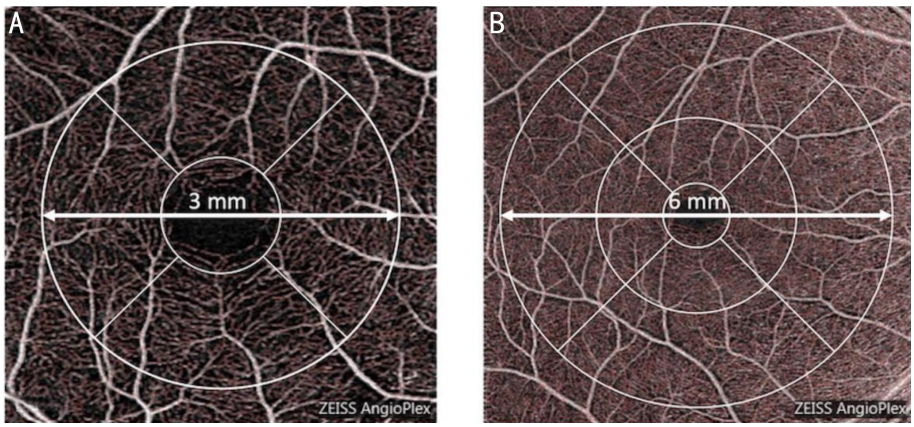

Figure 1 The schematic diagram of the optical coherence tomography angiography image, vessel density, and perfusion density were averaged over the area for each region. A: 3 mm×3 mm window. The inner circle is for the central region, which is for central vessel density (CVD) and central perfusion density (CPD); the area between the outer and inner circle is for the inner region, which is for inner VD (IVD) and inner PD (IPD); while the whole outer circle is for the full region, which is for full VD (FVD) and full PD (FPD); B: 6 mm× 6 mm window. The inner circle is for the central region, which is for CVD and CPD; the area between the inner and middle circle is for the inner region, which is for IVD and IPD; the area between the middle and outer circle is for the outer region, which is for outer VD (OVD) and outer PD (OPD); while the whole outer circle is for the full region, which is for FVD and FPD.

Table 1 Demographic and characteristics $\bar{x}\pm s$

Factors	Without DR (n=105)	DR (n=95)	P
Age (years)	46.6±10.1	53.1±10.2	<0.001[a]
FBG (mmol/L)	8.5±3.4	9.0±3.4	0.283
SBP (mmHg)	126.8±16.8	131.1±16.8	0.089
DBP (mmHg)	81.7±12.0	83.4±10.3	0.310
HbA1c (%)	9.0±2.4	9.9±2.5	0.012[a]
ALT (U/L)	26.7±19.7	23.1±13.2	0.141
AST (U/L)	19.9±12.0	18.6±8.0	0.471
ALP (U/L)	74.8±28.4	67.3±21.2	0.039[a]
Urea (mmol/L)	4.9±1.3	3.4±1.7	0.024[a]
Scr (μmol/L)	64.3±14.6	73.6±27.2	0.003[a]
Urea/Scr	19.4±5.6	18.9±5.7	0.565
DM duration (years)	3.9±4.3	7.0±6.0	<0.001[a]
HBP duration (years)	1.9±5.0	3.4±5.4	0.041[a]

[a]P<0.05. SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HbA1c: Glycosylated hemoglobin; FBG: Fasting blood glucose; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ALP: Alkaline phosphatase; Urea: Urinary albumin; Scr: Serum creatinine; DM: Diabetes mellitus; HBP: High blood pressure.

related diagnoses of the patients using RF, respectively (Figure 2A and 2B). For RF, it builds Bagging integration based on a decision tree (DT) and further introduces random attribute selection in the training process of DT. This method can effectively improve the classification accuracy of new samples. The randomness of the RF is reflected in the fact that the training samples for each tree are random, and the splitting properties of each node in the tree are randomly selected. With these two random factors, the RF stays within the bounds even if no pruning is performed on each DT. At first, we used the number of trees in an RF (ntree=500) to build both models. After the first round of model building was completed, we extracted the essential features from the first round of the modeling process. Afterwards, we adjusted the parameters of the two RF models, iterating over the ntree values from 1 to 500 to choose the best ntree value (ntree for biochemical indicators=268, ntree for other diagnoses=8). RF results are shown in Figure 2C-2F. For further analysis, 12 variables with a significance >6 and clinical significance were identified as candidate variables.

Establishment of diabetic retinopathy first diagnosis model According to the indicators selected by RF, the diagnostic model was established by LR (Table 2). A model incorporating the 12 potential predictors was developed and presented as the nomogram (Figure 3A).

Model performance On internal validation, the final diagnostic model had good discrimination, as demonstrated by the area under the ROC curve (AUC) of 0.819 and a Brier

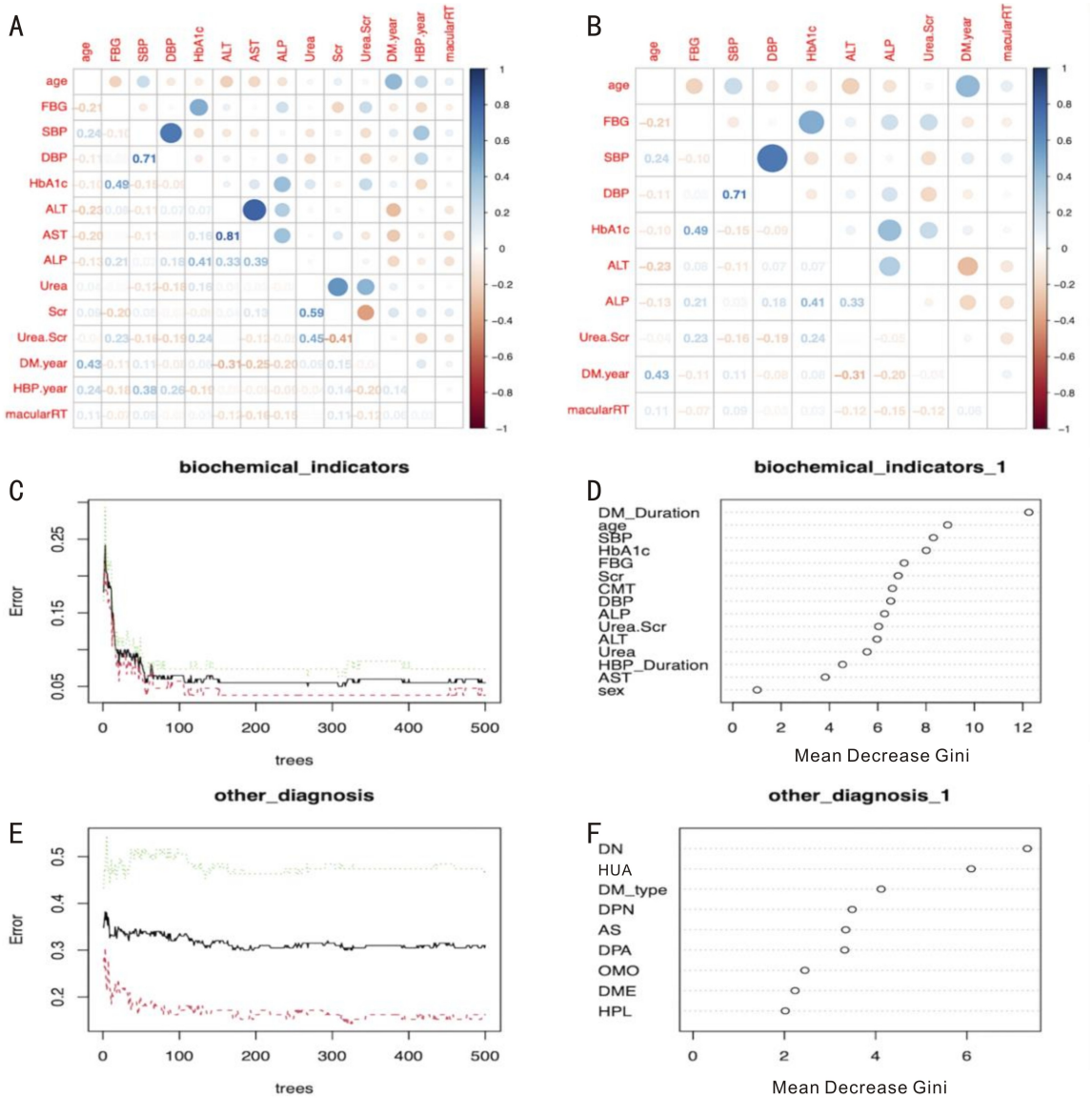

Figure 2 Characteristics of modeling variables. A: Correlation heat map between all biochemical variables; B: Correlation heat map between biochemical variables selected as modeling variables; C and E: The influence of the number of decision trees on the error rate; D and F: Results of the Gini coefficient method in the random forest classifier. SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HbA1c: Glycosylated hemoglobin; FBG: Fasting blood glucose; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ALP: Alkaline phosphatase; Urea: Urinary albumin; Scr: Serum creatinine; CMT: Central macular thickness; DME: Diabetic macular edema; OMO: Ocular media opacity; DN: Diabetic nephropathy; DPA: Diabetic peripheral vascular disease; DPN: Diabetic peripheral neuropathy; HUA: Hyperuricemia; AS: Atherosclerosis; HPL: Hyperlipidemia; HBP: High blood pressure; DM: Diabetes mellitus.

score of 0.172 (Figure 3B and 3C). The decision curve indicated that the diagnostic model has additional clinical value since it has the highest net benefit across a broad range of predicted probabilities ranging from 0% – 85% risk (Figure 3D). This suggests that basing decisions on the model will result in an overall net benefit compared to not using the model. It also achieved good bootstrap cross-validation performance (50 times 10-fold cross-validation, AUC=0.77).

Comparison of Optical Coherence Tomography Angiography Variables between Diabetic Retinopathy and Non-Diabetic Retinopathy Patients Inner vessel density (IVD), outer vessel density (OVD), Inner blood perfusion (IPD), and outer blood perfusion (OPD) of DR patients were significantly lower than those of patients without DR, regardless of whether it was in 3 mm×3 mm or 6 mm×6 mm window. In particular, in the 3 mm×3 mm window, CVD is significantly higher in non-DR patients but not observed in the 6 mm×6 mm window (Table 3; Figure 4).

Optical coherence tomography angiography improves the established diagnosis model After establishing a prediction model of DR diagnosis with good prediction performance, we explore how OCTA can improve the prediction performance of traditional prediction models. Therefore, based on the established factors (age, FBG, SBP, DBP, HbA1c, ALT, ALP, Urea/Scr, CMT, DM duration, HUA, DN), we added OCTA variables to the diagnostic model one by one and compared the AUC of new models (Figure 3E-3J). To quantify

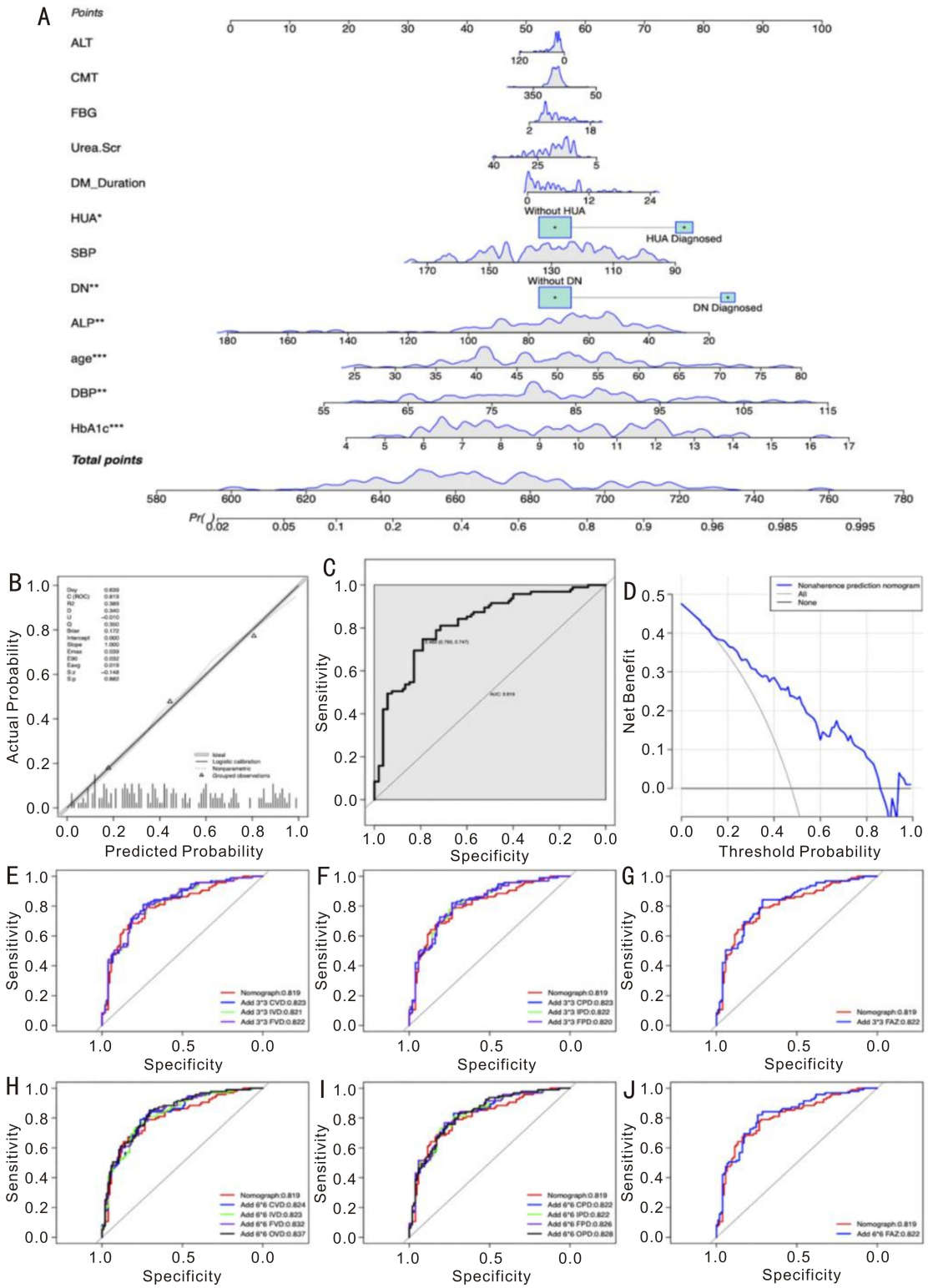

Figure 3 Nomogram and model performance of diagnostic andoptical coherence tomography angiography improved models. A: The first row (points) is assigned to each variable's measurement from rows 2-12, variables included in the predictive model. Assigned points for all variables are then summed, and the total can be located on line 13 (total points). Once total points are located, draw a vertical line down to the bottom line to obtain the predicted probability of DR; B: Calibration curve of the diagnostic nomogram to assess the predictive power of the nomogram model; C: ROC for diagnostic nomogram, AUC=0.819; D: The decision curve demonstrated that the diagnostic model has additional clinical value. E: The base model was combined with 3 mm×3 mm CDs, respectively; F: The base model was combined with 3 mm× 3 mm PDs, respectively; G: The base model was combined with 3 mm×3 mm FAZ; H: The base model was combined with 6 mm× 6 mm CDs, respectively; I: The base model was combined with 6 mm× 6mm PDs, respectively; J: The base model was combined with 6 mm× 6 mm FAZ. SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HbA1c: Glycosylated hemoglobin; FBG: Fasting blood glucose; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; Urea: Urinary albumin; Scr: Serum creatinine; CMT: Central macular thickness; DN: Diabetic nephropathy; HUA: Hyperuricemia; DM: Diabetes mellitus.

Table 2 Logistic prediction factors for diabetic retinopathy

Factors	Prediction model		
	OR	95%*CI*	*P*
Age	1.076	1.03-1.12	<0.001[a]
FBG	1.035	0.92-1.16	0.555
SBP	0.972	0.94-1.00	0.092
DBP	1.079	1.02-1.14	0.005
HbA1c	1.418	1.17-1.75	<0.001[a]
ALT	0.997	0.97-1.02	0.786
ALP	0.973	0.97-0.99	0.002[a]
Urea/Scr	0.974	0.91-1.04	0.432
DM Duration	1.047	0.97-1.14	0.267
CMT	0.998	0.99-1.01	0.708
HUA	3.209	1.33-8.20	0.011[a]
DN	4.760	1.59-15.85	0.007[a]

[a]*P*<0.05. FBG: Fasting blood glucose; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HbA1c: Glycosylated hemoglobin; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; Urea: Urinary albumin; Scr: Serum creatinine; DM: Diabetes mellitus; CMT: Central macular thickness; HUA: Hyperuricemia; DN: Diabetic nephropathy.

Table 3 Comparison of optical coherence tomography angiography variables $\bar{x}\pm s$

Parameters	Without DR	DR Diagnosed	*P*
3 mm×3 mm			
CVD	8.73±3.05	7.86±3.07	0.049[a]
IVD	20.51±2.03	19.53±2.20	0.002[a]
FVD	19.18±2.04	18.21±2.22	0.002[a]
CPD	0.15±0.05	0.14±0.05	0.087
IPD	0.37±0.03	0.36±0.04	0.013[a]
FPD	0.34±0.03	0.33±0.04	0.011[a]
FAZ	0.30±0.12	0.30±0.15	0.891
6 mm×6 mm			
CVD	7.76±2.80	6.97±3.43	0.076
IVD	17.35±1.79	16.44±2.54	0.004[a]
OVD	18.02±1.32	16.95±1.97	<0.001
FVD	17 58±1.37	16 56±2.05	<0 001
CPD	0.17±0.06	0.16±0.08	0.133
IPD	0.41±0.05	0.39±0.06	0.017[a]
OPD	0.45±0.03	0.42±0.05	<0.001
FPD	0.43±0.04	0.41±0.05	<0.001
FAZ	0.30±0.11	0.30±0.14	0.6367

[a]*P*<0.05. CVD: Central vascular density; IVD: Inner vascular density; OVD: Outer vascular density; FVD: Full vascular density; CPD: Central perfusion density; IPD: Inner perfusion density; OPD: Outer perfusion density; FPD: Full perfusion density; FAZ: Foveal avascular zone.

the improvement of the model, we introduce IDI to compare the models (Table 3). Later, we conducted RF on OVD and modeling variables together, and the importance of characteristics indicated that OVD in the 6 mm× 6 mm window ranked second only to DM duration (Figure 5A and 5B).

Performance of optical coherence tomography angiography improved model The improved model incorporating the 12 potential predictors and OVD in the 6 mm×6 mm OCTA window was developed and presented as the nomogram (Figure 5C). On internal validation, the OCTA-improved model had excellent discrimination, as demonstrated by an AUC of 0.837 and a Brier score of 0.166 (Figure 5D and 5E). Decision curves show that diagnostic models with additional clinical value have the highest net benefit in the 0%-90% risk prediction probability range. (Figure 5F). This suggests that basing decisions on the model will result in an overall net benefit compared to not using the model. It also achieved excellent bootstrap cross-validation performance (50 times 10-foldcross-validation, AUC=0.78).

Focus on the role of optical coherence tomography angiography in diabetic retinopathy screening of patients with diabetic nephropathy When focused on kidney indicators

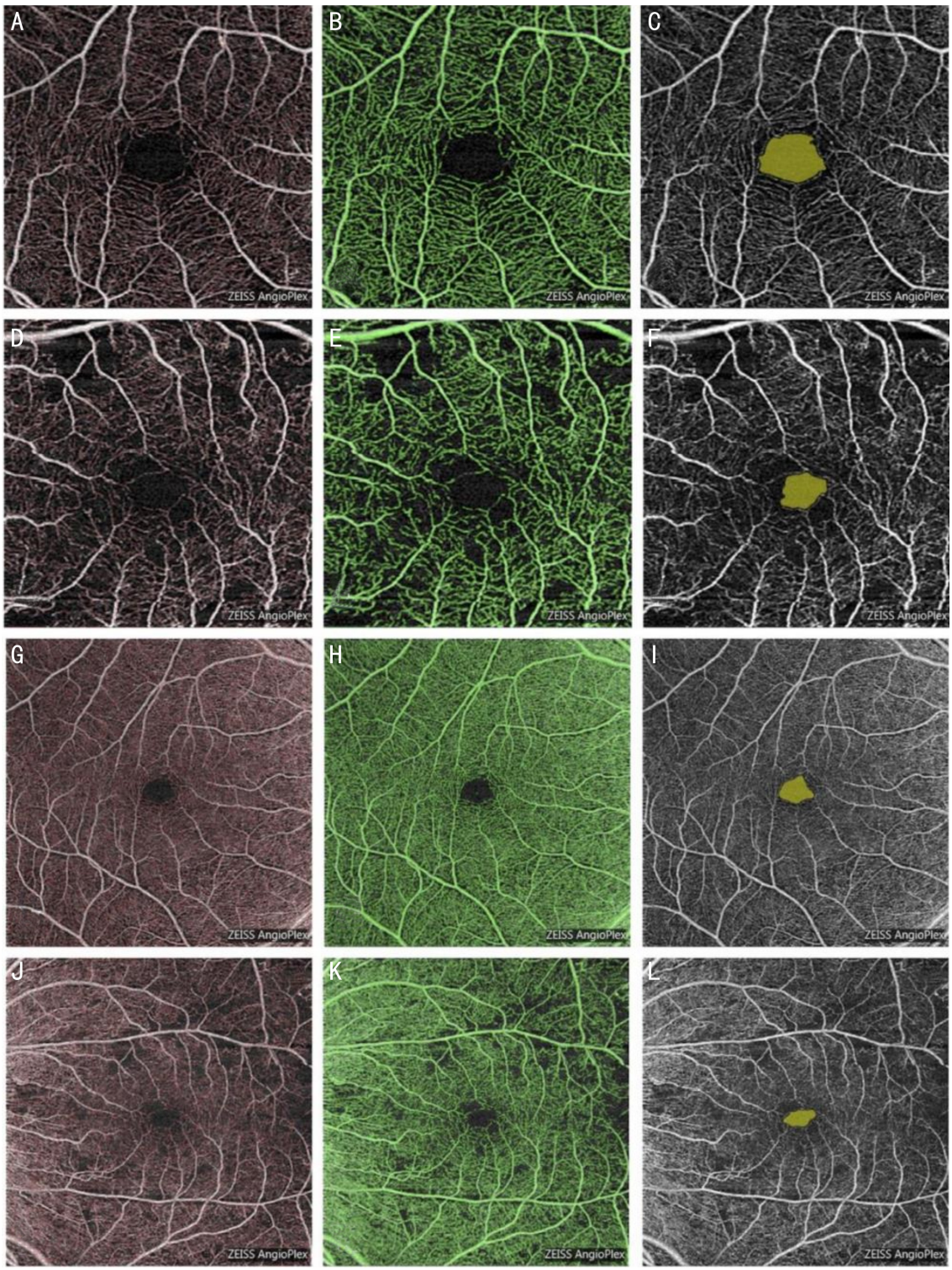

Figure 4 Comparison of vessel density and perfusion density of normal and nonproliferative diabetic retinopathy on optical coherence tomography angiography images. A: Normal VD in 3 mm×3 mm window; B: Normal PD in 3 mm× 3 mm window; C: Normal FAZ in 3 mm× 3 mm window; D: VD in 3 mm× 3 mm window for NPDR; E: PD in 3 mm× 3 mm window for NPDR; F: FAZ in 3 mm× 3 mm window for NPDR; G: Normal VD in 6 mm× 6 mm window; H: Normal PD in 6 mm×6 mm window; I: Normal FAZ in 6 mm× 6 mm window; J: VD in 6 mm×6 mm window for NPDR; K: PD in 6 mm× 6 mm window for NPDR; L: FAZ in 6 mm×6 mm window for NPDR. VD: Vessel density; PD: Perfusion density; FAZ: Foveal avascular zone; NPDR: Nonproliferative diabetic retinopathy.

closely related to DR and including three indicators (Urea/Scr, DN, and HUA) to establish a DR prediction model, the AUC indicated that this model's prediction efficiency was not ideal (AUC = 0.66). However, when we added OCTA parameters one by one to the model, the model's prediction performance was significantly improved, and the performance of the 6 mm×6 mm window was better than that of the 3 mm× 3 mm window (Table 3).

Table 3 Area under the curve and *P* value of integrated discrimination improvement for the optical coherence tomography angiography improved models

Parameters	Diagnostic model *vs* OCTA added models		Kidney focused model *vs* OCTA added models	
	AUC	P_{IDI}	AUC	P_{IDI}
3 mm×3 mm				
CVD	0.82	0.42	0.70	0.06
IVD	0.82	0.43	0.73	0.01[a]
FVD	0.82	0.40	0.73	0.01[a]
CPD	0.82	0.54	0.69	0.08
IPD	0.82	0.99	0.72	0.06
FPD	0.82	0.89	0.72	0.04[a]
FAZ	0.82	0.62	0.67	0.69
6 mm× 6 mm				
CVD	0.82	0.45	0.70	0.07
IVD	0.82	0.48	0.73	0.03[a]
OVD	0.83	0.03[a]	0.78	<0.01[a]
FVD	0.84	0.08	0.77	<0.01[a]
CPD	0.82	0.54	0.70	0.11
IPD	0.82	0.71	0.73	0.09
OPD	0.83	0.21	0.76	<0.01[a]
FPD	0.83	0.33	0.75	<0.01[a]
FAZ	0.82	0.58	0.66	0.86

[a]$P<0.05$. OCTA: Optical coherence tomography angiography; AUC: Area under the curve; IDI: Integrated discrimination improvement; CVD: Central vascular density; IVD: Inner vascular density; OVD: Outer vascular density; FVD: Full vascular density; CPD: Central perfusion density; IPD: Inner perfusion density; OPD: Outer perfusion density; FPD: Full perfusion density; FAZ: Foveal avascular zone.

DISCUSSION

In this study, we developed a diagnostic prediction model for DR with good predictive performance, and the performance of the conventional DR prediction model was significantly improved when the OVD in 6 mm×6 mm window was added. In addition, we further elucidated the significance of the microvascular parameters of the 6 mm × 6 mm window for screening DR in patients with DN. Compared with the gold standard fluorescent angiography for evaluating the DR vascular system, OCTA shows the advantages of excellent non- invasive capture of the fundus vascular micro lesions[12-15]. More importantly, OCTA provides a means to evaluate the vascular changes in different retinal capillary clusters. Compared with those without DR, the first diagnosed DR patients have significantly lower IVD, OVD, IPD, and OPD measured by OCTA, consistent with previous studies[16]. This result is consistent with the pathophysiology of DR, with low retinal VD reflecting early vascular damage in the preclinical phase of DR[17-19], ultimately leading to retinal capillary detachment[20]. Additionally, the VD in the DCP beside the central fovea of NPDR patients was significantly reduced, and the FAZ area remained unchanged[21], which also confirmed our results. In general, fundamental retinal blood flow changes lead to insufficient retinal perfusion in the early stage of DR[22], which is also the reason for the significant decrease in PD.

This study provides hard evidence to prove the predictive value of OCTA indicators for the early diagnosis of DR. After adding the OVD of the 6 mm× 6 mm window, the traditional DR diagnostic model was significantly improved, and the new model performed satisfactorily. It is speculated that the changes in the distal hemodynamics of microvessels may occur first, leading to changes in the density and perfusion of peripheral distal vessels. The occurrence of such changes can also more sensitively predict the incidence of DR. The advantage of the study is to predict the contribution of OCTA to DR diagnosis by including patients with an initial diagnosis who have not accepted any DR-related treatment. Previous studies have provided dozens of high-quality pieces of evidence to prove that OCTA indicators can be used to predict the progress of DR. The research shows that FAZ, VD, and fractal dimension (FD) predict the progression of DR, while VD of SCP is related to the DME progress[10]. Further, FAZ and PVD are predictors of DR progress, improving the risk assessment of DR progress compared with the separately identified risk factors[23]. Studies have shown that vascular skeletal density (VSD) significantly improves the clinical discrimination between DR and PDR compared to age, gender, and other diabetes-related complications. However, these prospective studies were limited to patients with severe DR, such as PDR. Our study focused on the preclinical exploration of DR and provided strong evidence for the early diagnosis of DR.

Microvascular complications occurring during DM are widespread, affecting multiple organ systems throughout the body, including the retina, kidneys, and heart. DR and DN

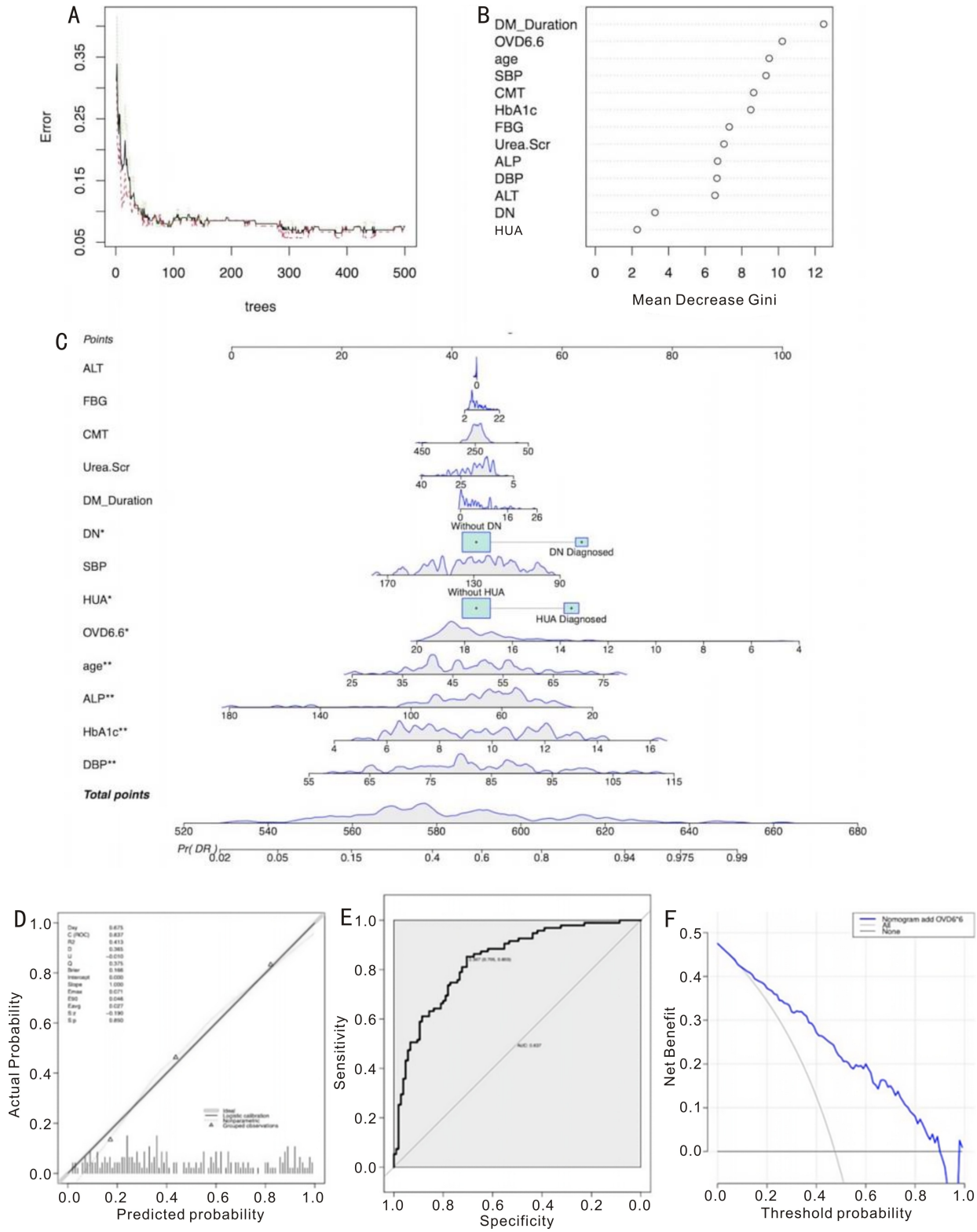

Figure 5 Nomogram and model performance of kidney focused diagnostic, and optical coherence tomography angiography improved models. A: We applied the best ntree value (ntree=306); B: RF results are shown. The DM duration ranked the highest importance, and the importance decreased in order; C: The first row (points) is assigned to each variable's measurement from rows 2-13, variables included in a predictive model. Assigned points for all variables are then summed, and the total can be located online 14 (total points). Once total points are located, draw a vertical line down to the bottom line to obtain the predicted probability of DR; D: Calibration curve of the diagnostic nomogram to assess the predictive power of the OCTA improved model; E: ROC for diagnostic nomogram, AUC=0.837; F: The decision curve demonstrated that the diagnostic model has additional clinical value.SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HbA1c: Glycosylated hemoglobin; FBG: Fasting blood glucose; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; Urea: Urinary albumin; Scr: Serum creatinine; CMT: Central macular thickness; DN: Diabetic nephropathy; HUA: Hyperuricemia; OVD: Outer vascular density; DM: Diabetes mellitus.

share similar pathophysiologic mechanisms and are often detected by clinicians simultaneously[24]. Therefore, the development of one may signal an increased risk of the other. Prior fluorescein angiography requires intravenous injection of dye, which may increase renal burden and have the potential to increase the risk of adverse events. In patients with severe renal disease who have renal insufficiency, the kidneys may not be able to completely clear fluorescein angiography, resulting in an increased risk of nephrotoxicity. As a non-invasive detection based on blood flow motion detection, OCTA may be a better method for screening DN patients for DR. On this basis, we further explored the role of OCTA in improving DR prediction models, focusing on renal-related indicators.

HUA is the leading risk factor of renal damage in DM, and together with HBP and HPL, it promotes the occurrence and development of DN[25-26]. Meanwhile, the uric acid excretion rate in PDR patients was significantly lower than that in NPDR patients[27]. Recently, accumulated evidence points out that HUA is closely related to DR. The concentration of uric acid in the vitreous cavity of the DM group was significantly higher than that of the control group, which was positively correlated with the severity of DR. It is speculated that the increase of vitreous uric acid concentration maybe related to the dysfunction of the blood-retinal barrier in DR patients[28]. The increased blood uric acid accumulates in the vitreous through the dysfunctional blood-retinal barrier, causing retinal vascular damage, thus promoting the progress of DR. In the exploration of microvascular diseases, OCTA can play its advantages in providing high-quality retinal VD and PD information. When these minor microvascular diseases are captured, the high risk of DN or DR can be predicted before clinical treatment, thus providing a space for pre-clinical intervention, which has far-reaching significance for the prevention and management of microvascular complications in DM. In addition, the results show that compared with the information provided by the 3 mm×3 mm window, the VD and PD information given by the 6 mm×6 mm window is more sensitive to the changes of microvessels. To clarify, the plentiful information about the end of microvessels given by a broader field of vision is a more sensitive indicator of early lesions.

The strength of this study lies in exploring the role of OCTA in improving the predictive performance of conventional DR prediction models for patients with a first diagnosis of NPDR who have never received any appropriate ophthalmic treatment and for patients without DR. Second, based on patients' biochemical parameters and other diagnoses, combined with OVD, the most sensitive OCTA variables for predicting DR, this study constructed a comprehensive predictive scoring system with far-reaching clinical value. In addition, this study also focuses on renal function indicators, which provide an interactive bridge between DN and DR screening and contribute to better management of DM. In conclusion, the information on microvascular changes provided by OCTA not only significantly improves the traditional prediction model of DR by keenly capturing early vascular changes in the retina, but also contributes to the establishment of a network of DN monitoring in diabetic patients, which, through noninvasive and safe means, can comprehensive and in-depth detection of microvascular complications of diabetes. Limitations include the fact that DR was determined by single-field fundus photography, some DR cases may have been missed or DR severity may have been misclassified, and the small sample size in our current study. Second, we included only eyes with high-quality images, which may have introduced selection bias and limited the generalizability of the results. Therefore, the significance of this study in clinical applications deserves further exploration and validation in subsequent large-sample clinical studies.

Conflicts of Interest: Yang XY, None; Yi GG, None; Chen YX, None; Yang SY, None; Ai SB, None; Zheng C, None; Cao MZ, None; Fu M, None.

Authors' contributions: Yang XY: Data Processing; Wrote the Paper; Yi GG: Wrote the Paper; Chen YX: Drafting the Text; Yang SY: Preparing the Figures; Ai SB: Revise the Paper; Zheng C: Revise the Paper; Cao MZ: Data Collection; Fu M: Design the Research; Revise the Paper.

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