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Correlations of serum hypoxia-inducible factor 1α, vascular endothelial growth factor, and stromal cell-derived factor-1 levels with microvascular injury in patients with proliferative diabetic retinopathy

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ABSTRACT

Background: Proliferative diabetic retinopathy (PDR) is characterized by pathological neovascularization and microvascular damage driven by hypoxia-related mechanisms. We aimed to explore the correlations of serum hypoxia-inducible factor 1α (HIF-1α), vascular endothelial growth factor (VEGF), and stromal cell-derived factor-1 (SDF-1) levels with microvascular injury in patients with proliferative diabetic retinopathy.

Methods: Subjects (150 in total) with type 2 diabetes mellitus and diabetic retinopathy (DR) who were treated at our hospital between January 2023 and June 2024 were assigned to a proliferative DR (PDR) group (n=82) and a non-proliferative DR (NPDR) group (n=68). Comparisons were carried out on the general data, microvascular endothelial function [circulating endothelial cells (CEC), endothelial progenitor cells (EPC), and circulating progenitor cells (CPC)], and serum HIF-1α, VEGF and SDF-1 between the two groups.

Results: High expressions of serum HIF-1α, VEGF, and SDF-1 were associated with an increased risk of PDR of 2.465, 3.132, and 2.592 times, respectively ($p<0.05$). Serum HIF-1α, VEGF, and SDF-1 were independent influencing factors for PDR ($p<0.05$). Areas under the curves (AUCs) of serum HIF-1α, VEGF, and SDF-1 for predicting PDR were 0.721, 0.762, and 0.748, respectively. A prediction model combining serum HIF-1α, VEGF, and SDF-1 was constructed: Log(P) =-0.251 + 0.271 × HIF-1α + 0.290 × VEGF + 0.277 × SDF-1. AUCs of the triple combination for PDR prediction was 0.869, significantly exceeding the predictive values of the three indicators alone (Z=3.246, 3.172, 3.231, p=0.002, <0.001, <0.001).

Conclusions: Serum HIF-1α, VEGF, and SDF-1 have significant correlations with microvascular injury in proliferative diabetic retinopathy patients, and their combination is highly valuable for the early identification of high-risk patients.

Keywords: correlation, diabetic retinopathy, hypoxia-inducible factor 1α, microvascular injury, stromal cell-derived factor-1

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INTRODUCTION

According to statistics, about 90 million out of the 468 million patients with diabetes mellitus (DM) in the world suffer from varying degrees of DR. It is estimated that there will be approximately 191 million patients by 2030, including nearly one-third of PDR, which is the leading cause of visual impairment and blindness in DM patients [1,2]. Since microvascular injury is the most typical feature of PDR, finding out the serum markers related to microvascular injury and timely taking effective intervention measures are the key to PDR prevention and treatment [3]. HIF-1α is an endogenous signaling protein. Bilgin et al. [4] conducted relevant serum tests on DR patients and found that HIF-1α was overexpressed and probably affected the formation of microvascular injury. VEGF cannot only promote endothelial cell growth and vessel lumen formation, but also exacerbate a series of pathological changes like retinal ischemia and hypoxia, which are closely associated with the condition of DR [5]. SDF-1 can participate in DR development and progression by regulating inflammatory response, angiogenesis, and migration [6]. The detection of microvascular endothelial function indicators (such as circulating endothelial cells, endothelial progenitor cells, and circulating progenitor cells) requires professional personnel and equipment, and it is time-consuming and hard to be popularized. By contrast, serum indicators can be examined through standardized laboratory processes, so it is suitable for large-scale clinical screening or dynamic testing. Moreover, previous clinical studies have paid attention to changes of the above indicators in DR [7,8].

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On this basis, the present study intended to explore the correlations of serum HIF-1α, VEGF and SDF-1 with microvascular injury in PDR patients as well as the significance of their combination in predicting PDR, aiming to provide new monitoring indicators and methods for the clinical identification of high-risk patients.

METHODS

Study participants

A total of 150 DR patients treated from January 2023 to June 2024 were selected in our hospital according to the following inclusion criteria: 1) patients with type 2 DM (T2DM) and meeting the diagnostic criteria of DR [9], 2) those with monocular lesions, 3) those with regular medications and stable glucose control, 4) those aged >18 years old, and 5) those who actively participated in this study. The exclusion criteria were applied to 1) patients with complications of DM in addition to DR, 2) those who had recently taken drugs affecting microvascular endothelial function, 3) those with other ocular diseases, 4) those with retinopathy due to mechanical impact, hypertension, or other factors, 5) those with a history of ocular trauma or intraocular surgery, 6) those with lesions of vital organs, or 7) those with acute/chronic infectious diseases or immune system diseases.

The present study was completed in accordance with the Declaration of Helsinki developed by the World Medical Association and was approved by the ethics committee of Qingdao Hospital, University of Health and Rehabilitation Sciences, Shandong Province, China (approval date: January 5th, 2023). All the enrolled patients signed the informed consent. Subsequently, a PDR group (n=82) and a non-PDR (NPDR) group (n=68) were established to assign the patients based on the type of retinopathy.

Data collection and laboratory investigations

The general data, including gender, age, course of DM, smoking history, drinking history, fasting plasma glucose (FPG), 2 h postprandial plasma glucose (2-h PG), and glycosylated hemoglobin A1c (HbA1c) were collected. FPG and 2-h PG were measured by the glucose oxidase method using an automated biochemistry analyzer (Hitachi 7100, Japan), and HbA1c was determined by high-performance liquid chromatography using an automated HbA1c analyzer (Maccura G01, China).

Serum HIF-1α, VEGF, and SDF-1 plus microvascular endothelial function were detected. Specifically, 3 mL of peripheral venous blood were collected from every subject in plain tubes, kept for 30 min, and centrifuged for 10 min at 4,000 rpm. Afterwards, the serum was aspirated to determine HIF-1α, VEGF, and SDF-1 through enzyme-linked immunosorbent assay equipped with kits purchased from Beijing Solarbio Science & Technology Co., Ltd (HIF-1α: SEKH-0434; VEGF: SEKH-0052; SDF-1: SEKH-0310).

Flow cytometric analysis of circulating endothelial cells (CEC), endothelial progenitor cells (EPC), and circulating progenitor cells (CPC) was performed following previously published protocols for rare-event detection. Peripheral EDTA-anticoagulated blood (100 µL) was processed within 2 hours. Red blood cells were lysed using ammonium-chloride lysis buffer (Thermo Fisher Scientific, USA) for 10 min at room temperature, followed by centrifugation (300 × g, 5 min) and washing with PBS containing 1% BSA. After lysis, nucleated cells were resuspended in 100 µL staining buffer and incubated with fluorochrome-conjugated monoclonal antibodies for 20 min in the dark. The antibody panel included FITC anti-CD45 (clone HI30, BD Biosciences, USA), PE anti-CD34 (clone 581, BD, USA), APC anti-CD133 (clone AC133, Miltenyi Biotec, Germany), and PE-Cy7 anti-VEGFR2/KDR (clone 89106, R&D Systems, USA). APC-Cy7 anti-CD146 (clone P1H12, BD, USA) was used for endothelial identification. Matched isotype controls and fluorescence-minus-one controls were included to set negative thresholds. After staining, cells were washed and resuspended in 300 µL of PBS/BSA.

For absolute quantification, 10 µL of CountBright™ absolute counting beads (Thermo Fisher Scientific, USA) were added immediately before acquisition. Samples were acquired on a BD flow cytometer (FACSCount) using fixed PMT voltages and daily cytometer calibration beads. A minimum of 300,000 total nucleated events were collected per sample to ensure reliable detection of rare populations. Gating was performed according to established rare-event strategies. Debris and doublets were excluded using FSC/SSC and FSC-A/FSC-H. CD45bright leukocytes were excluded. CEC were defined as CD45–CD34+CD146+ events. EPC were defined as CD45dimCD34+CD133+VEGFR2+ cells, while CPC were defined as CD45dimCD34+CD133+/- cells. Absolute counts (cells/µL blood) were calculated from the ratio of cell events to bead events. Data were analyzed using FlowJo (v10).

Evaluation of indicators

The observation indicators in the two groups included general data, microvascular endothelial function, serum HIF-1α, VEGF, and SDF-1, the correlations of serum HIF-1α, VEGF and SDF-1 with microvascular endothelial function, the influences of serum HIF-1α, VEGF and SDF-1 on PDR, and the predictive value of serum HIF-1α, VEGF and SDF-1 for PDR.

Statistical analysis

SPSS 27.0 software (IBM, USA) was utilized for statistical analysis. Measurement data conforming to normal distribution were shown in the format of mean ± stand-

ard deviation (x ± s) and examined by the t-test. For the comparison of categorical (quantitative) data between groups, the chi-squared (χ^2) test was used. Pearson correlation analysis and multivariate logistic regression analysis were performed. Relative risk (RR) analysiss was employed to assess the risk. Receiver operating characteristic (ROC) curves were plotted to analyze the diagnostic efficiency, and AUC >0.700 was considered indicative of predictive efficiency. Statistical significance threshold was set at $p<0.05$.

RESULTS

General data and microvascular endothelial function

PDR group had a longer course of DM, more CEC, and fewer EPC and CPC than the NPDR group ($p<0.05$) (Table 1).

Serum HIF-1α, VEGF, and SDF-1

Serum HIF-1α, VEGF, and SDF-1 levels were higher in the PDR group compared the NPDR group ($p<0.05$) (Figure 1).

Table 1. General data and microvascular endothelial function parameters

Indicator	PDR group (n=82)	NPDR group (n=68)	χ2/t	*p* value
Gender	–	–	0.614	0.433
Male	51 (62.2%)	38 (55.9%)	–	–
Female	31 (37.8%)	30 (44.1%)	–	–
Age (years)	61.2 ± 7.4	59.9 ± 6.8	1.136	0.258
Smoking history (years)	17.2 ± 1.7	16.6 ± 2.2	1.829	0.070
Drinking history (years)	24.1 ± 1.9	23.9 ± 2.2	0.589	0.557
Diabetes mellitus history (years)	12.2 ± 2.4	9.8 ± 2.2	6.230	<0.001
Fasting plasma glucose (mmol/L)	7.41 ± 0.54	7.28 ± 0.51	1.505	0.134
2-h plasma glucose (mmol/L)	8.57 ± 0.75	8.36 ± 0.72	1.738	0.084
HbA1c (%)	7.54 ± 0.62	7.44 ± 0.60	0.998	0.320
Circulating endothelial cells (%)	0.147 ± 0.030	0.091 ± 0.020	13.155	<0.001
Endothelial progenitor cells (%)	0.036 ± 0.007	0.049 ± 0.010	9.335	<0.001
Circulating progenitor cells (%)	0.092 ± 0.012	0.143 ± 0.017	21.476	<0.001

Results are expressed either as n (%) or mean ± standard deviation.

Table 2. Correlations of serum HIF-1α, VEGF, and SDF-1 with microvascular endothelial function

Index	Circulating endothelial cells (CEC)		Endothelial progenitor cells (EPC)		Circulating progenitor cells (CPC)	
	r	*p* value	r	*p* value	r	*p* value
HIF-1α	0.624	<0.001	-0.653	<0.001	-0.634	<0.001
VEGF	0.671	<0.001	-0.702	<0.001	-0.690	<0.001
SDF-1	0.654	<0.001	-0.629	<0.001	-0.661	<0.001

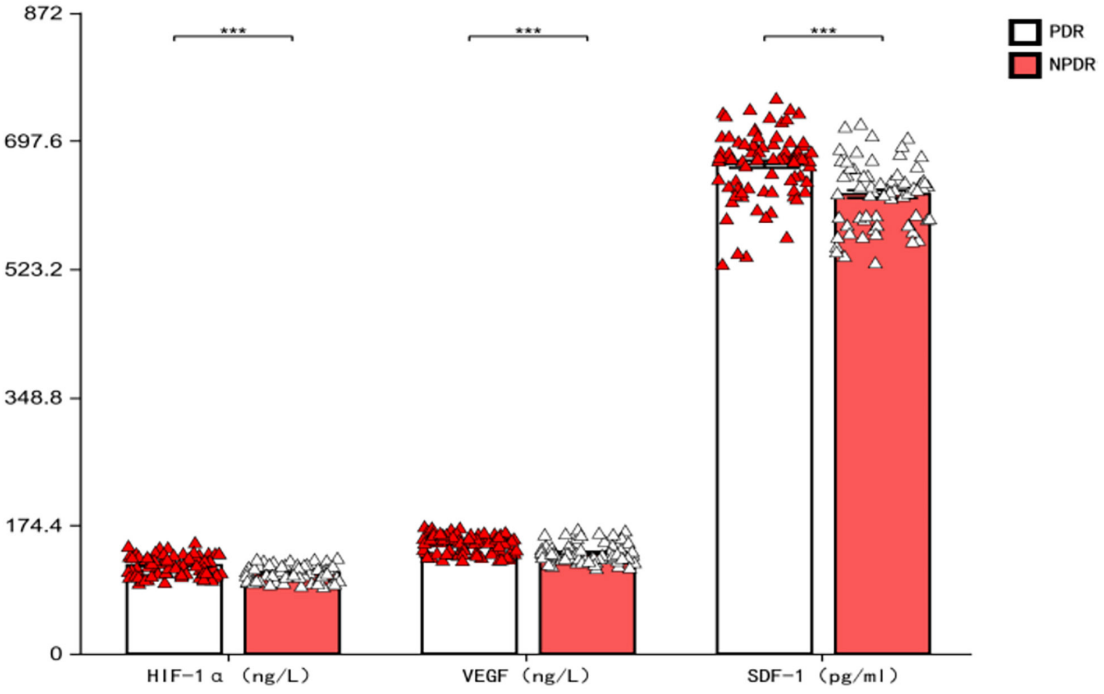

Figure 1. Serum HIF-1α, VEGF and SDF-1. *** indicates a statistically significant difference

Correlation analysis revealed that serum HIF-1α, VEGF, and SDF-1 had positive associations with CEC but negative relations to EPC and CPC (p<0.05) (Table 2).

Impact of serum HIF-1α, VEGF, and SDF-1 on PDR

With the mean level as the cutoff value, serum HIF-1α, VEGF, and SDF-1 in the two groups of patients were defined as lowly expressed and highly expressed. As revealed by RR analysis, high expressions of serum HIF-1α, VEGF, and SDF-1 enhanced the risk of PDR by 2.465 [95% confidence interval (CI): 1.318-4.529], 3.132 (95% CI: 1.570-6.014), and 2.592 (95% CI: 1.336-4.962) times, respectively (p<0.05) (Table 3).

Logistic regression analysis on serum biomarkers

With the presence or absence of PDR as a dependent variable (presence = 1, absence = 0), and the course of DM (input as actual value), HIF-1α (input as actual value), VEGF (input as actual value), SDF-1 (input as actual value), CEC (input as actual value), EPC (input as actual value), and CPC (input as actual value) as independent variables, logistic regression analysis uncovered that all

Table 3. Impact of serum HIF-1α, VEGF, and SDF-1 on PDR

Indicator		PDR group (n=82)	NPDR group (n=68)	RR (95% CI)	U	*p* value
HIF-1α	Low expression	33	49	2.465 (1.318 – 4.529)	2.683	0.006
	High expression	49	19			
VEGF	Low expression	16	45	3.132 (1.570 – 6.014)	3.192	0.007
	High expression	66	23			
SDF-1	Low expression	29	56	2.592 (1.336 – 4.962)	2.746	0.001
	High expression	53	12			

Table 4. Results of logistic regression analysis on serum HIF-1α, VEGF, and SDF-1 plus microvascular injury

Variable	β	Standard error	Wald χ2	Odds ratio	95% confidence interval	*p* value
HIF-1α	0.271	0.056	23.420	1.311	1.256 – 1.369	<0.001
VEGF	0.290	0.049	34.291	1.336	1.262 – 1.414	<0.001
SDF-1	0.277	0.051	29.476	1.319	1.258 – 1.383	<0.001
Constant	-0.254	0.071	12.145	–	–	<0.001

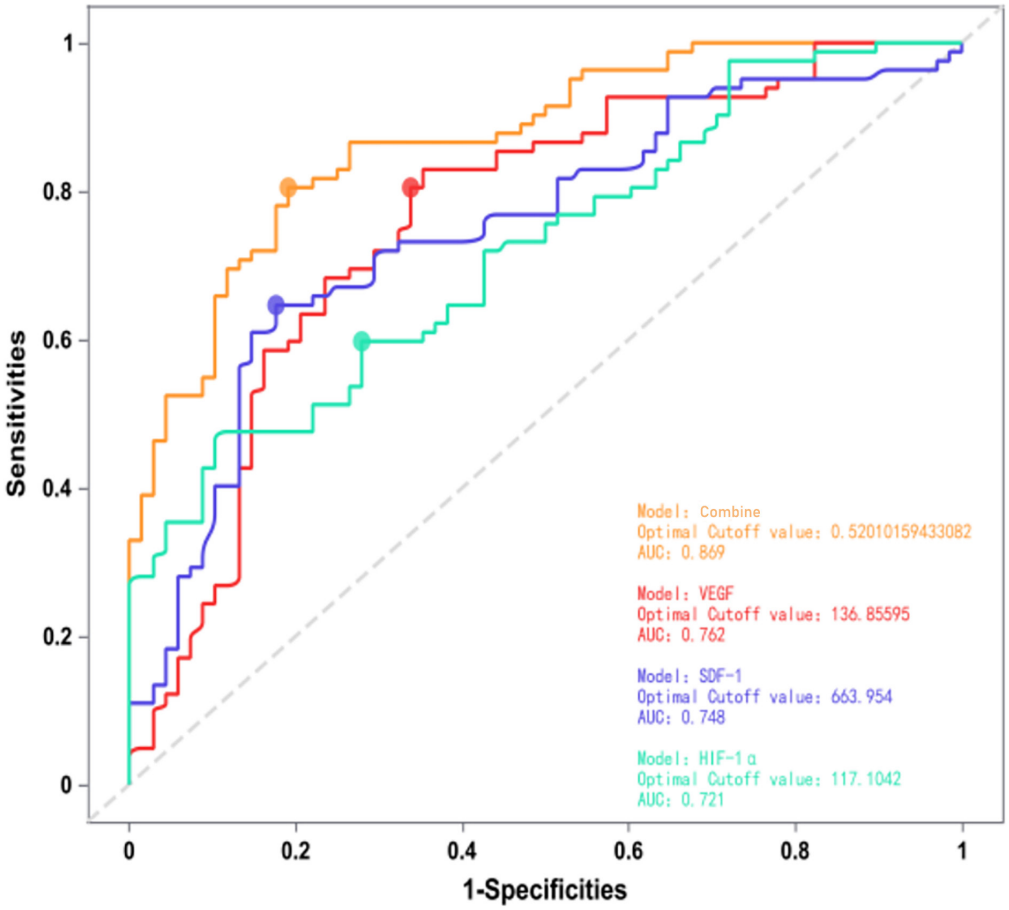

Figure 2. ROC curves of serum HIF-1α, VEGF and SDF-1 for predicting PDR

these indicators were independent influencing factors for PDR (p<0.05). After that, such factors as PDR severity, CEC, EPC, and CPC were adjusted, and logistic regression analysis was conducted with the independent variables of serum HIF-1α, VEGF, and SDF-1, which were found to remain as the independent influencing factors for PDR (p<0.05) (Table 4).

Predictive value of HIF-1α, VEGF, and SDF-1 for PDR

ROC curves were plotted by virtue of source data (serum HIF-1α, VEGF and SDF-1), negative data samples (NPDR patients), and positive data samples (PDR patients). As for PDR prediction, serum HIF-1α, VEGF, and SDF-1 had AUCs of 0.721, 0.762, and 0.748, sensitivity of 59.76%, 80.49%, and 64.63%, and specificity of 72.06%, 66.18%, and 82.35%, respectively. Later, a prediction model combined with serum HIF-1α, VEGF, and SDF-1 was constructed based on logistic regression model 2, namely, Log(P) =-0.251 + 0.271 × HIF-1α + 0.290 × VEGF + 0.277 × SDF-1. The AUC of the triple combination for PDR prediction was 0.869, together with the sensitivity of 80.49% and specificity of 80.88%, significantly higher than those of individual indicators (Z=3.246, 3.172, 3.231; and p=0.002, <0.001, <0.001, respectively) (Figure 2).

DISCUSSION

DR may occur in 20%-40% of adult patients with T2DM and it may progress to PDR in severe cases, leading to visual disability and blindness [10]. Therefore, seeking relevant indicators for early prediction of PDR has become a focus of research on the prevention and treatment of this disease. HIF-1α is a specific transcription factor produced by cells under the stimulation of ischemia and hypoxia, of which the abnormal expression is intimately associated with multiple DM-induced organ injuries [11]. Serum HIF-1α level in DR patients is in significant relation to risk factors such as HbA1c and systolic blood pressure [12]. In the retina of DM rats, the expression of HIF-1α expression climbs remarkably at week 12 of the disease course, accompanied by vascular disorders and neovascularization, proving its involvement in the pathological process of DR in the early stage [13]. Such a phenomenon was also observed in this study, and multivariate analysis manifested that increased HIF-1α served as an independent risk factor for PDR, regardless of whether other interference factors were adjusted or not. Based on analysis of relevant data [14,15], HIF-1α has a dual effect on PDR. On the one hand, HIF-1α facilitates the release of inflammatory factors through activating the NF-κB pathway, exacerbates blood-retinal barrier injury, induces the expression of oxidative stress-related enzymes, and promotes retinal cell apoptosis. On the other hand, it can up-regulate VEGF, boost pathological angiogenesis, lead to abnormal structure of new blood vessels, and aggravate microvascular leakage and hemorrhage, thus accelerating the progression of PDR. It is recommended that clinical attention should be paid to detecting the changes of HIF-1α in the serum of DR patients in order to facilitate early identification of high-risk patients. Targeted modulation of HIF-1α expression level or signaling pathways (e.g., combination with SGLT2 inhibitors and anti-VEGF drugs) has significant potential for improving DR [16]. Hence, more relevant studies can be carried out in the future to achieve precision treatment.

Metabolism disorders like hyperglycemia can cause ocular hypoxia and inflammation and stimulate the overexpression of VEGF, especially VEGF-A. VEGF is a core driver of the pathological process of DR, and its abnormal elevation is directly associated with DR vascular leakage, neovascularization, and visual impairment [17,18]. Loporchio et al. [19] also reported that VEGF rose gradually in patients with T2DM, NPDR, and PDR. On this basis, the relationship between VEGF and PDR was innovatively analyzed in the present study, and VEGF increase was found to be a major high-risk factor for the disease (OR=1.336). The associated mechanisms are as follows [20,21]. First, VEGF can bind to corresponding receptors to exert promoting effects on vascular permeability and neovascularization, thus destroying the blood-retinal barrier. Second, VEGF is capable of directly acting on the FIt-1/KDR pathway to result in leukocyte stasis and inflammatory cell infiltration, trigger inflammatory response, and worsen retinal ischemia and hypoxia. Third, VEGF can mediate mitochondrial oxidative stress, activate and damage retinal vascular endothelial cells, thicken vascular basement membrane, and increase microvascular permeability, leading to retinal vascular endothelial dysfunction. It can be seen that VEGF is involved in microvascular injury through various mechanisms, thereby promoting the evolution of DR to PDR. As a result, serum VEGF can serve as a marker of PDR and its further progression, rendering a reference for early prediction of PDR and understanding of its mechanism in clinical practice.

SDF-1 is a crucial player in the occurrence and development of DM as well as its complications, and its mechanism involves the protection of pancreatic islet function, vascular repair, and regulation of organ injury. The concentration of SDF-1 is prominently raised in the vitreous body of patients as DR progresses to PDR, and SDF-1 level has positive correlations with the area of neovascularization and the degree of fibrous membrane proliferation [22]. In the present study, the serum SDF-1 level in patients with PDR and NPDR was detected. The results manifested that SDF-1 was evi-

dently higher in PDR patients than in NPDR patients, and it was related to microvascular endothelial function, suggesting that SDF-1 plays an important role in the pathological process of DR. Furthermore, it was indicated that the risk of PDR was incremented with the rising SDF-1 level. The reason is that SDF-1 binds to its receptor CXCR4 to activate downstream signaling pathways, induce the migration of vascular endothelial cells to the ischemic retina, and initiate abnormal vascular proliferation. Meanwhile, it can stimulate macrophages, monocytes, and other inflammatory cells to infiltrate the retina, thus destroying the blood-retinal barrier [23]. Through an animal model of DR [24], it was discovered that SDF-1 and VEGF expressions are synchronously elevated, and their combination can accelerate retinal vascular leakage and structural damage. Taken together, SDF-1 and VEGF can be dynamically monitored as biomarkers for assessing DR activity, and they are of particular significance in early warning of high-risk patients, which can become a direction for subsequent research.

According to the results of the present study, the AUCs of HIF-1α, VEGF, and SDF-1 alone for predicting PDR were 0.721, 0.762, and 0.748, respectively, all of which exceeded 0.7 and signified certain predictive efficiency. Besides, the combination of the three indicators had an AUC of 0.869 for PDR prediction, which was greater than that of individual indicators, presenting markedly increased predictive efficiency. Consequently, when the cutoff values of serum HIF-1α, VEGF, and SDF-1 reach 117.104 ng/L, 136.855 ng/L, and 663.954 pg/mL, respectively, relevant prevention and treatment schemes should be actively formulated, and interventions should be promptly implemented to prevent further deterioration of disease, thus ameliorating patients' prognosis.

Nevertheless, this study is limited. The subjects were mainly recruited from populations in the same region, without consideration of the wide territory of China, so it is necessary to conduct nationwide multi-center studies to further validate the clinical value of HIF-1α, VEGF, and SDF-1 in PDR patients.

CONCLUSIONS

In conclusion, serum HIF-1α, VEGF, and SDF-1 are significantly associated with microvascular injury in PDR patients, and their combination is highly valuable in predicting PDR, which can provide a reliable basis for identification of PDR patients in clinical practice.

ABBREVIATIONS

AUC – area under the curve

CEC – circulating endothelial cells

CPC – circulating progenitor cells

DR – diabetic retinopathy

EPC – endothelial progenitor cells

HIF-1α – hypoxia-inducible factor 1α

PDR – proliferative diabetic retinopathy

ROC – receiver operating characteristic

RR – relative risk

SDF-1 – stromal cell-derived factor-1

T2DM – type 2 diabetes mellitus

VEGF – vascular endothelial growth factor

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AUTHORS' CONTRIBUTION

FL: study design, investigation, data collection.

YG: resources, data analysis, writing.

All authors have read and approved the final version of the manuscript.

CONFLICT OF INTEREST

None to declare.

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