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INFLUENCE OF CHANGES IN SERUM LEVELS OF IL-1F4, INCAM-1 AND VPF ON PATIENTS WITH DIABETIC RETINOPATHY

UTICAJ PROMENA SERUMSKIH NIVOA IL-1F4, ICAM-1 I VPF KOD PACIJENATA SA DIJABETIČKOM RETINOPATIJOM

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Summary

Background: To explore the relationships between serum Interleukin-1 family member 4 (IL-1F4), Intercellular adhesion molecule-1 on endothelial cells (INCAM-1), and Vascular Permeability Factor (VPF) levels and disease progression and prognosis in patients with diabetic retinopathy (DR).
Methods: Five hundred thirty-eight individuals with type 2 diabetes mellitus (T2DM) who were admitted to our hospital between February 2022 and February 2025 were chosen retrospectively. Based on their DR outcomes, these patients were divided into two groups: 178 with T2DM and 360 with DR. The evolution of these DR patients' illnesses led to further division into two groups: a non-PDR (NPDR) group (134 instances) and a proliferative DR (PDR) group (226 cases). Additionally, 134 healthy volunteers who underwent examinations during the same time frame comprised the control group. The differences in clinical data and serum levels of IL-1F4, INCAM-1, and VPF among the different groups were compared; the correlations among serum levels of IL-1F4, INCAM-1, and VPF were analysed, and to determine the variables affecting the course of DR. Based on the occurrence of visual impairment, DR patients were divided into two groups after a year of follow-up: those with a favourable prognosis (256 patients) and those with a poor progno-

Kratak sadržaj

Uvod: Cilj je bio da se ispita povezanost između serumskih nivoa interleukina-1 člana porodice 4 (IL-1F4), intercelularnog adhezionog molekula-1 na endotelnim ćelijama (INCAM-1) i faktora vaskularne permeabilnosti (VPF) sa progresijom bolesti i prognozom kod pacijenata sa dijabetičkom retinopatijom (DR).
Metode: Retrospektivno je odabrano 538 osoba sa dijabetes melitus tipom 2 (T2DM) koje su bile hospitalizovane u našoj bolnici u periodu od februara 2022. do februara 2025. godine. Na osnovu ishoda DR, pacijenti su podeljeni u dve grupe: 178 pacijenata sa T2DM i 360 pacijenata sa DR. U skladu sa razvojem bolesti, pacijenti sa DR su dalje podeljeni u grupu sa neproliferativnom dijabetičkom retinopatijom (NPDR, 134 slučaja) i grupu sa proliferativnom dijabetičkom retinopatijom (PDR, 226 slučajeva). Pored toga, 134 zdrava dobrovoljca pregledana u istom vremenskom periodu su činila kontrolnu grupu. Upoređene su razlike u kliničkim podacima i serumskim nivoima IL-1F4, INCAM-1 i VPF među različitim grupama; analizirane su korelacije između serumskih nivoa IL-1F4, INCAM-1 i VPF, kao i faktori koji utiču na tok DR. Nakon jednogodišnjeg praćenja, pacijenti sa DR su, prema pojavi oštećenja vida, podeljeni na grupu sa povoljnom prognozom (256 pacijenata) i grupu sa lošom prognozom (104 pacijenta). Upoređene su razlike u kliničkim

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sis (104 patients). Differences in clinical data and serum levels of IL-1F4, INCAM-1, and VPF among DR patients with different prognoses were compared. The factors influencing the poor prognosis of diabetic retinopathy (DR) were identified using multivariate logistic regression. The predictive value of serum IL-1F4, INCAM-1, and VPF for poor DR prognosis was assessed using receiver operating characteristic (ROC) curves.

Results: The fasting blood glucose (FPG), glycosylated haemoglobin (HbA1c), IL-1F4, INCAM-1, and VPF levels in the control group, T2DM group, NPDR group, and PDR group increased successively (P<0.05), and the duration of diabetes in the T2DM group, NPDR group, and PDR group increased successively (P<0.05). The serum levels of IL-1F4, INCAM-1, and VPF in individuals with DR showed positive relationships (r=0.500, 0.489, and 0.564, respectively; P<0.05) according to Pearson analysis. High levels of FPG, HbA1c, IL-1F4, INCAM-1, and VPF, together with a longer duration of diabetes, were found to influence the progression of DR (P<0.05) in a multivariate logistic regression analysis. Groups with poor prognoses were older than those with good prognoses. Body mass index, FPG, HbA1c, IL-1F4, INCAM-1, and VPF were higher in the group with a poor prognosis than in the group with a good prognosis. Additionally, the duration of diabetes was longer in the poor prognosis group (P<0.05). Multivariate logistic regression analysis revealed that a longer duration of diabetes, as well as high levels of FPG, HbA1c, IL-1F4, INCAM-1, and VPF, were all variables affecting how DR progressed (P<0.05). The areas under the curve (AUCs) for forecasting a bad prognosis in individuals with diabetic retinopathy (DR) were found using ROC curve analysis. According to serum levels of IL-1F4, INCAM-1, and VPF were 0.771, 0.823, and 0.766, respectively. When these three indicators were combined, the area under the curve (AUC) for predicting a poor prognosis in DR patients was 0.873, which was higher than the AUC for any one sign alone (P<0.05).

Conclusion: Serum IL-1F4, INCAM-1 and VPF may jointly participate in the process of DR. The elevated levels of these cytokines are closely related to the progression of DR and poor prognosis. Serum IL-1F4, INCAM-1, and VPF can serve as effective indicators of DR progression and visual disability.

Keywords: type 2 diabetes, diabetic retinopathy, interleukin-1 family member 4, intercellular adhesion molecule-1 on endothelial cells, vascular permeability factor, prognostic analysis

podacima i serumskim nivoima IL-1F4, INCAM-1 i VPF između pacijenata sa različitom prognozom. Faktori koji utiču na lošu prognozu dijabetičke retinopatije identifikovani su multivarijantnom logističkom regresijom. Prediktivna vrednost serumskih nivoa IL-1F4, INCAM-1 i VPF za lošu prognozu DR procenjena je pomoću ROC krivih.

Rezultati: Nivoi glukoze u krvi natašte (FPG), glikozilovanog hemoglobina (HbA1c), IL-1F4, INCAM-1 i VPF sukcesivno su rasli u kontrolnoj grupi, T2DM grupi, NPDR grupi i PDR grupi (P<0,05), dok se trajanje dijabetesa sukcesivno povećavalo u T2DM, NPDR i PDR grupama (P<0,05). Pirsonova analiza je pokazala pozitivnu korelaciju između serumskih nivoa IL-1F4, INCAM-1 i VPF kod pacijenata sa DR (r=0,500, 0,489 i 0,564; P<0,05). Multivarijantna logistička regresiona analiza pokazala je da su visoki nivoi FPG, HbA1c, IL-1F4, INCAM-1 i VPF, kao i duže trajanje dijabetesa, faktori koji utiču na progresiju DR (P<0,05). Pacijenti sa lošom prognozom su bili stariji od pacijenata sa dobrom prognozom. Indeks telesne mase, FPG, HbA1c, IL-1F4, INCAM-1 i VPF su bili viši u grupi sa lošom prognozom nego u grupi sa dobrom prognozom. Takođe, trajanje dijabetesa je bilo duže u grupi sa lošom prognozom (P<0,05). Multivarijantna logistička regresiona analiza je pokazala da su duže trajanje dijabetesa i visoki nivoi FPG, HbA1c, IL-1F4, INCAM-1 i VPF faktori koji utiču na progresiju DR (P<0,05). Analiza ROC krive je pokazala da su površine ispod krive (AUC) za predviđanje loše prognoze kod pacijenata sa DR na osnovu serumskih nivoa IL-1F4, INCAM-1 i VPF iznosile 0,771, 0,823 i 0,766. Kada su ova tri pokazatelja kombinovana, AUC za predviđanje loše prognoze kod pacijenata sa DR je iznosio 0,873, što je bilo više od AUC vrednosti bilo kog pojedinačnog pokazatelja (P<0,05).

Zaključak: Serumski IL-1F4, INCAM-1 i VPF mogu zajednički učestvovati u procesu razvoja DR. Povišeni nivoi ovih citokina su tesno povezani sa progresijom DR i lošom prognozom. Serumski IL-1F4, INCAM-1 i VPF mogu služiti kao efikasni pokazatelji progresije DR i nastanka oštećenja vida.

Ključne reči: dijabetes melitus tip 2, dijabetička retinopatija, interleukin-1 član porodice 4, intercelularni adhezioni molekul-1 na endotelnim ćelijama, faktor vaskularne permeabilnosti, prognostička analiza

Introduction

Type 2 diabetes mellitus (T2DM) is among the leading causes of visual impairment and blindness worldwide. The most prevalent microvascular consequence of type 2 diabetes is diabetic retinopathy (DR), which poses a major risk to patients' visual health and quality of life (1). The rising global prevalence of T2DM has rendered DR a significant public health concern (2). The development and course of DR are influenced by several complex pathophysiological mechanisms, including chronic hyperglycaemia, oxidative stress, the inflammatory response, and abnormal expression of angiogenic factors (3). In-depth research into the pathogenesis of DR and the identification of effective biomarkers to assess disease progression and prognosis are crucial for developing personalised treatment strategies and improving patient outcomes. Inflammation's function in the onset and progression of DR has garnered a lot of attention in recent years. One multipurpose proinflammatory cytokine is Interleukin-1 family member 4 (IL-1F4), which is widely involved in inflammatory responses and immune regulation. Studies have shown that IL-1F4 levels are closely associated with the occurrence and progression of microvascular complications in T2DM patients and may participate in the pathologic process of DR through mechanisms such as inducing vascular endothelial apoptosis and increasing vascu-

lar permeability (4). Intercellular adhesion molecule-1 on endothelial cells (INCAM-1) is an important cell surface adhesion molecule that mediates the adhesion of white blood cells to vascular endothelial cells and plays a key role in inflammatory responses and vascular injury. Studies have shown that INCAM-1 expression in retinal vascular endothelial cells of DR patients is significantly upregulated and that INCAM-1 may be involved in the inflammatory response and vascular injury processes in DR (5). One important component that controls angiogenesis and permeability is Vascular Permeability Factor (VPF), and it plays an important role in the pathological process of DR. Studies have shown that abnormal elevation of VPF in DR patients can damage the blood–retinal barrier, increase vascular permeability, cause retinal oedema and neovascularisation, and ultimately lead to visual impairment (6).

Examining the changes in blood levels of VPF, INCAM-1, and IL-1F4 in people with diabetic retinopathy (DR) and their relationships to the course and outcome of the illness are the goals of this study.

Materials and Methods

General information

Five hundred thirty-eight T2DM patients admitted to our hospital between February 2022 and February 2025 were retrospectively selected. Depending on the patients' DR complication status, they were divided into two groups: 178 cases of T2DM and 360 cases of DR. Additionally, these DR patients were further divided into two groups based on the course of their disease: a non-PDR (134 instances) group and a proliferative DR (PDR) group (226 cases).

The control group consisted of 134 additional healthy volunteers who were examined physically in the hospital during the same time period, and our hospital's ethics committee approved this study (No. A0293).

Inclusion criteria: ① All pertinent diagnostic requirements were satisfied. All cases of DR were unilateral, and the »International Guidelines for the Prevention and Management of Type 2 Diabetes (2022 Edition)« (7) served as the basis for the T2DM diagnostic criteria, whilst the »Expert Consensus on the Prevention and Treatment of Diabetic Retinopathy«served as the basis for the DR diagnostic criteria (8); ② age was no less than 18 years; and ③ complete clinical data and follow-up data were available.

Exclusion criteria: ① individuals with malignant tumours; ② those with significant organ dysfunction; ③ those with acute or chronic infections; ④ those with a history of intraocular surgery or ocular trauma; ⑤ those with other eye diseases, such as glaucoma, uveitis, age-related macular degeneration, and cataracts; ⑥ individuals with other types of diabetes; ⑦ critically ill patients or those at the end stage of various diseases; and ⑧ patients who already have visual impairment upon admission.

Clinical data collection

Detailed information about the subjects, including sex, age, BMI, history of hypertension, history of smoking, duration of diabetes, blood pressure, blood glucose levels (fasting blood glucose (FPG) and glycosylated haemoglobin (HbA1c)), and blood lipid levels (total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C)).

Serum index detection

Four millilitres of fasting venous blood were obtained from all individuals. After blood separation, the serum levels of INCAM-1 and VPF were determined using a BN100 automatic analyser and the corresponding reagents from the American Dade Behring Company. An enzyme-linked immunosorbent test kit from Jiangsu Pu Yuan Biotechnology Co., Ltd. was used to determine the serum level of IL-1F4.

Prognostic follow-up

All patients received standardised treatment (7–9) and were followed up for 12 months through telephone, outpatient visits, and the internet. The criteria for assessing visual disability were as follows: low vision (visual disability grades 1–2) or blindness (visual disability grades 3–4), based on the best single-eye vision. Based on the presence of visual impairment, patients with diabetic retinopathy were split into two groups: those with a good prognosis (128 patients) and those with a poor prognosis (52 patients).

Statistical methods

SPSS 22.0 was used to analyse the data. Gender, hypertension, smoking history, and other count data are expressed as instances (%), and the χ^2 test was used to examine group differences. Age, BMI, length of diabetes, and other normally distributed data are expressed as $\bar{x}\pm s$. T tests were used to compare the two groups, and one-way analysis of variance was used to compare the groups. The correlations among serum IL-1F4, INCAM-1, and VPF levels were analysed using the Pearson correlation coefficient. To investigate the factors contributing to the progression of diabetic retinopathy (DR) and its unfavourable prognosis, multivariate logistic regression was used. Serum levels of VPF, INCAM-1, and IL-1F4 were evaluated for their prognostic value in DR patients using receiver operating characteristic (ROC) curves.

Results

Comparison of clinical data and serum levels of IL-1F4, INCAM-1, and VPF in each group

The levels of FPG, HbA1c, IL-1F4, INCAM-1, and VPF increased successively in the control, T2DM, NPDR, and PDR groups (P<0.05). The duration of diabetes in the T2DM, NPDR, and PDR groups increased in a stepwise manner (P<0.05). The PDR, NPDR, and T2DM groups had higher percentages of hypertension, TC, TG, HDL-C, and LDL-C than the control group (P<0.05). The other clinical data did not show any statistically significant differences between the groups (P>0.05; see *Table I*).

Table I Comparison of clinical data and serum levels of IL-1F4, INCAM-1, and VPF among groups ($\bar{x}\pm s$, n (%)).

Item	PDR group (n=226)	NPDR group (n=134)	T2DM group (n=178)	Control group (n=134)	F/x^2	P
Age/years	56.06±7.84	55.24±10.34	54.86±7.65	55.67±8.57	0.315	0.810
BMI/(kg/m^2)	24.90±2.42	25.23±2.83	25.64±2.77	26.19±1.85	3.497	0.019
Gender					0.487	0.922
Male	130 (57.52)	74 (55.22)	94 (52.81)	76 (56.72)		
Female	96 (42.48)	60 (44.78)	84 (47.19)	58 (43.28)		
Hypertension					13.656	0.003
Yes	42 (18.58)	22 (16.42)	28 (15.73)	0		
No	184 (81.42)	112(83.58)	150 (84.27)	134 (100.00)		
Smoking history					1.241	0.744
Yes	102 (45.13)	54 (40.30)	78 (43.82)	50 (37.31)		
No	124 (54.87)	80 (59.70)	100 (56.18)	84 (62.69)		
Systolic blood pressure/mmHg	138.49±22.68	140.12±24.56	140.74±24.50	139.59±24.07	0.167	0.924
Course of diabetes/ year	10.12±2.79	9.16±2.35	7.19±1.54	-	43.655	<0.001
TC/(mmol/L)	5.39±0.47	5.28±0.61	4.88±0.55	3.66±0.79	138.762	<0.001
TG/(mmol/L)	1.95±0.30	1.97±0.32	1.74±0.44	1.29±0.32	48.183	<0.001
HDL-C/(mmol/L)	1.01±0.10	1.02±0.12	1.23±0.23	1.35±0.25	24.744	<0.001
LDL-C/(mmol/L)	3.22±0.91	3.29±0.69	2.84±0.41	2.27±0.47	35.954	<0.001
FPG/(mmol/L)	10.37±1.50	9.76±1.72	8.94±1.29	4.92±0.62	218.645	<0.001
HbA1c/%	9.42±1.39	8.91±1.47	7.79±1.53	5.14±0.68	170.477	<0.001
L-18/(pg/mL)	133.21±34.10	112.33±28.20	92.99±22.51	69.61±18.97	83.521	<0.001
INCAM-1/(pg/mL)	642.32±70.22	598.44±86.55	544.74±69.17	305.32±28.70	370.877	<0.001
VPF/(pg/mL)	272.45±21.40	262.76±18.32	247.63±17.79	120.39±15.47	1040.229	<0.001

Table II Correlation between serum IL-1F4, INCAM-1, and VPF levels in DR patients.

Item		IL-1F4	INCAM-1	VPF
IL-1F4	r	-	0.500	0.489
	P	-	<0.001	<0.001
INCAM-1	r	0.500	-	0.564
	P	<0.001	-	<0.001
VPF	r	0.489	0.564	-
	P	<0.001	<0.001	-

Table III Multivariate logistic regression analysis of factors affecting the progression of DR disease.

Variable	B	SE	Wald	P	OR	95%CI
Course of diabetes	0.318	0.124	6.757	0.002	1.373	1.083~1.739
FPG	-0.48	0.225	4.118	0.046	0.631	0.416~0.988
HbA1c	0.444	0.187	5.756	0.019	1.558	1.087~2.233
IL-1F4	0.025	0.013	5.151	0.026	1.026	1.006~1.045
INCAM-1	0.001	0.007	3.929	0.041	1.000	1.003~1.017
VPF	0.021	0.016	4.330	0.030	1.021	1.005~1.058

Correlations among the serum levels of IL-1F4, INCAM-1 and VPF in DR patients

Pearson correlation analysis indicated a positive association among the serum levels of IL-1F4, INCAM-1, and VPF in patients with diabetic retinopathy (r=0.500, 0.489, 0.564; P<0.05, respectively; see *Table II*).

Multivariate logistic regression analysis of factors influencing the progression of DR

According to multivariate logistic regression analysis, factors associated with the progression of DR included high fasting plasma glucose (FPG), high HbA1c, a longer history of diabetes, and elevated levels of VPF, INCAM-1, and IL-1F4 (P<0.05; see *Table III*).

Comparison of clinical data and serum levels of IL-1F4, INCAM-1, and VPF in patients with different prognoses of DR

The members of the bad prognosis group were older than those in the good prognosis group, and their BMI, FPG, HbA1c, IL-1F4, INCAM-1, and VPF levels were greater than those of the good prognosis group. Compared to the group with a good prognosis, the poor prognosis group had diabetes for a longer period of time (P<0.05), see *Table IV*.

Multivariate logistic regression analysis of the variables influencing diabetic retinopathy patients' poor prognosis

Multivariate logistic regression analysis indicated that prolonged diabetes duration, elevated fasting plasma glucose (FPG), increased HbA1c, and heightened levels of IL-1F4, INCAM-1, and VPF were determinants of adverse prognosis in individuals with diabetic retinopathy (P<0.05), see *Table V*.

Value of serum IL-1F4, INCAM-1 and VPF in predicting the prognosis of DR

According to the results of the ROC curve analysis, the areas under the curve (AUCs) for predicting a poor prognosis in patients with DR based on serum levels of VPF, INCAM-1, and IL-1F4 were 0.771, 0.823, and 0.766, respectively. With an area under the curve (AUC) of 0.873, which was greater than that of any single indicator (P<0.05), all three

Table IV Comparison of clinical data and serum IL-1F4, INCAM-1, VPF levels in DR patients with different prognoses (%).

Item	Good prognosis group (n=256)	Poor prognosis group (n=104)	t/x^2	P
Age/Year	53.98±8.51	60.13±7.85	4.460	<0.001
BMI/(kg/m^2)	24.63±2.45	26.11±2.76	3.825	<0.001
Gender			0.252	0.614
Male	142 (55.47)	62 (59.62)		
Female	114 (44.53)	42 (40.38)		
Hypertension			0.573	0.453
Yes	42 (16.41)	22 (21.15)		
No	21 4 (83.59)	82 (78.85)		
Smoking history			0.034	0.863
Yes	112 (43.75)	44 (42.31)		
No	144 (56.25)	60 (57.69)		
Systolic blood pressure/ mmHg	138.29±23.16	141.12±23.89	0.767	0.448
Course of diabetes/year	8.98±2.34	11.93±2.26	7.842	<0.001
TC/(mmol/L)	5.35±0.53	5.36±0.63	0.143	0.882
TG/(mmol/L)	1.96±0.30	1.94±0.43	0.376	0.702
HDL-C/(mmol/L)	1.13±0.11	1.07±0.12	1.952	0.055
LDL-C/(mmol/L)	3.28±0.83	3.38±1.07	0.729	0.461
FPG/(mmol/L)	9.72±1.61	10.93±1.32	4.193	<0.001
HbAlc/%	8.88±1.10	10.43±1.39	7.684	<0.001
IL-1F4/(pg/mL)	116.37±30.05	147.97±31.54	6.301	<0.001
INCAM-1/(pg/mL)	601.70±72.25	685.73±63.57	7.301	<0.001
VPF/(pg/mL)	262.88±17.89	283.42±20.52	6.717	<0.001

Table V Multivariate logistic regression investigation of determinants influencing worse outcomes in diabetic retinopathy.

Variable	B	SE	Wald	P	OR	95% CI
Age	-0.001	0.040	2.232	0.138	0.936	0.855~1.025
BMI	0.010	0.148	0.017	0.908	1.011	0.769~1.355
Course of diabetes	0.389	0.114	12.152	<0.001	1.474	1.187~1.820
FPG	-0.502	0.247	4.349	0.030	0.604	0.376~0.973
HbAlc	0.945	0.295	10.368	0.001	2.567	1.448~4.542
IL-1F4	0.010	0.002	3.880	0.042	1.010	1.002~1.038
INCAM-1	0.026	0.009	13.430	<0.001	1.026	1.014~1.039
VPF	0.068	0.023	10.842	0.001	1.060	1.020~1.102

Table VI The value of serum IL-1F4, INCAM-1, and VPF levels in predicting poor prognosis in DR patients.

Item	AUC	SE	P	95%CI	Cutoff value	Youden index	Sensitivity	Specificity
IL-1F4	0.771	0.031	<0.001	0.706~0.856	160.800 pg/mL	0.459	0.551	0.891
INCAM-1	0.823	0.039	<0.001	0.753~0.893	679.258 pg/mL	0.542	0.599	0.956
VPF	0.766	0.045	<0.001	0.685~0.848	284.258 pg/mL	0.529	0.599	0.933
Joint diagnostic model	0.873	0.020	<0.001	0.810~0.927	0.319	0.682	0.762	0.923

indicators together predicted a poor prognosis in DR patients, see *Table VI*.

Discussion

Diabetes is a metabolic disease marked by consistently elevated blood sugar levels, which can lead to complications in multiple bodily systems (10). The number of people worldwide aged 20 to 79 years who have diabetes has reached 536.6 million, accounting for 10.5% of the population in this age group (11). This figure is particularly alarming. The number of diabetes patients is as high as 140.9 million, ranking first globally, and the vast majority of them are T2DM patients. DR is a common microvascular complication for patients with T2DM. On the basis of its pathological characteristics, it can be classified into PDR and NPDR. Among them, PDR causes particularly significant damage to visual function and is the main factor leading to vision loss in T2DM patients. Although the medical community has continuously researched DR in more depth, the exact pathogenesis of DR has not yet been fully clarified, and the current treatment methods still have limitations in terms of effectiveness (12). Therefore, identifying indicators that can predict the progression of early-stage DR and evaluating its prognosis are highly important for clinical practice.

A long-term high blood sugar environment induces pathological changes in retinal microvessels, causing ischemia and hypoxia in local tissues. These changes subsequently trigger a series of inflammatory cascades. This series of reactions not only aggravates damage to the blood–retina barrier but also promotes the apoptosis of retinal nerve cells, thereby accelerating the deterioration of DR (13). Studies have shown that multiple inflammatory mediators are closely related to the occurrence and development of DR. These inflammatory mediators (including but not limited to INCAM-1 and IL-1F4) play important roles in the pathophysiology of DR (14). IL-1F4, a multifunctional proinflammatory cytokine, is integral to the initiation and regulation of inflammatory responses, further enhancing and sustaining inflammation by inducing the expression of inflammatory mediators, including chemokines, adhesion molecules, and interferon-γ (15). INCAM-1, a key cell surface adhesion molecule, mainly mediates the adhesion process between white blood cells and vascular endothelial cells and plays an important role in the recruitment and infiltration of inflammatory cells. Under high glucose conditions, retinal vascular endothelial cells are damaged (16). The serum levels of IL-1F4 and INCAM-1 in the PDR group were greater than those in the NPDR group and the T2DM group, and high serum levels of IL-1F4 and INCAM-1 were factors influencing disease progression and poor prognosis in DR patients. These findings suggest that IL-1F4 and INCAM-1 are involved in the occurrence and development of DR. According to these results, persistently elevated blood glucose levels are the primary cause of DR development and occurrence. They can also encourage the buildup of advanced glycation end products and trigger the elevation of IL-1F4 and INCAM-1 expression. High blood sugar can further amplify the inflammatory response and vascular damage by inducing oxidative stress and mitochondrial dysfunction, forming a vicious cycle and accelerating the progression of DR (17). IL-1F4 is a multifunctional proinflammatory cytokine that can induce the generation of inflammatory mediators such as interferon-γ, thereby amplifying the inflammatory cascade. It can promote the apoptosis of vascular endothelial cells, increase vascular permeability, and damage the integrity of the blood–retina barrier, leading to pathological changes such as retinal oedema and haemorrhage (18). INCAM-1 main function is to mediate the adhesion of white blood cells to vascular endothelial cells, promoting the infiltration of inflammatory cells into the local retina and thereby exacerbating the inflammatory response. INCAM-1 can also participate in oxidative stress responses, inducing retinal cell damage and apoptosis and aggravating the pathological damage caused by DR (19).

The pathological features of DR include structural and functional abnormalities of the retinal vascular system. In the early stage of DR, retinal capillary endothelial cells are damaged, resulting in increased vascular permeability and changes in

hemodynamic. As the disease progresses, the degree of retinal ischemia and hypoxia intensifies, triggering a series of compensatory pathological physiological responses. Among them, pathological neovascularisation is an important indicator for DR to enter the proliferative stage. These neovascular structures are abnormal, with fragile walls, and are prone to leakage and rupture, often causing serious complications (20). In DR, chronic hyperglycaemia leads to retinal microvascular lesions, causing local ischemia and hypoxia and subsequently stimulating the excessive secretion of VPF by retinal cells (such as retinal pigment epithelial cells and Müller cells) (21). In this study, the serum VPF level in the PDR group was greater than that in the NPDR group and the T2DM group, and a high serum VPF level was an influencing factor for disease progression and poor prognosis in DR patients. These findings suggest that VPF can increase the risk of disease progression and poor prognosis in DR patients (22). In addition, VPF can downregulate the expression of intercellular junction proteins (such as ZO-1 and occludin) between vascular endothelial cells, disrupt the integrity of the blood–retinal barrier, and increase vascular permeability, leading to retinal oedema and exudation. VPF-induced vascular leakage is among the main pathological mechanisms of diabetic macular oedema and severely damages the central vision of patients (23).

The serum levels of IL-1F4, INCAM-1, and VPF in DR patients were positively correlated. The positive correlation among these three factors reflects the mutual promotion of inflammation, vascular damage, and angiogenesis during the pathological process of DR, together driving the progression of DR. This mechanism provides an important basis for the multitarget combined treatment of DR. The results suggest that IL-1F4 induces the production of inflammatory mediators such as IFN-γ and TNF-α, amplifying the inflammatory response and thereby promoting the expression of INCAM-1 and VPF. INCAM-1 mediates the adhesion of white blood cells to vascular endothelial cells, promoting the infiltration of inflammatory cells and indirectly stimulating the secretion of VPF. VPF not only directly promotes angiogenesis but also increases vascular permeability and induces the expression of inflammatory factors, further amplifying the inflammatory response and forming a vicious cycle between inflammation and angiogenesis (24). During the pathological process of DR, IL-1F4 and INCAM-1 promote the inflammatory response and vascular damage, providing a pathological basis for the activity of VPF, whereas VPF promotes angiogenesis and increases vascular permeability, further exacerbating the inflammatory response and vascular damage (25). Higher fasting plasma glucose (FPG) and higher HbA1c levels were all factors influencing the progression and poor prognosis of DR. The results of this analysis suggest that the longer the duration of diabetes is, the higher the FPG and HbA1c levels, the greater the risk of poor blood glucose control, the more severe the condition is, and the risk of poor prognosis is greater (26–28). Serum IL-1F4, INCAM-1, and VPF levels for poor prognosis in patients with DR had the highest AUC, indicating that the prognostic value for a bad prognosis in individuals with DR can be enhanced by the simultaneous detection of all three signs.

Conclusion

Serum IL-1F4, INCAM-1 and VPF may jointly participate in the process of DR. The development of DR and a bad prognosis are strongly correlated with the increased levels of these genes. Serum IL-1F4, INCAM-1 and VPF can be used as effective indicators for evaluating the progression of DR and visual disability.

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Conflict of interest statement

All the authors declare that they have no conflict of interest in this work.

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