Original Article
Correlation between serum IL-22 and IL-27 levels and vasculopathy in diabetic nephropathy patients

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Abstract: Objective: To explore the correlation between serum interleukin-22 (IL-22) and interleukin-27 (IL-27) levels and vasculopathy in patients with diabetic nephropathy (DN). Methods: A total of 104 DN patients treated at the Shanxi University of Traditional Chinese Medicine Affiliated Hospital were selected as the observation group, with another 104 healthy individuals, serving as the control group in this retrospective study. The baseline data and the serum levels of IL-22 and IL-27 were compared between the two groups. The observation group was divided into three subgroups based on their urinary albumin excretion rate (UAER): clinical albuminuria group (microangiopathy, 29 patients), microalbuminuria group (51 patients), and normal albuminuria group (24 patients). Logistic regression was used to analyze the factors influencing the occurrence of microangiopathy. According to whether they had major adverse cardiovascular events (MACE) during 6-month follow-up, the DN patients were divided into a MACE group (n = 39) and a non-MACE group (n = 65). The serum levels of IL-22 and IL-27 were then compared between the two groups. The clinical utility of IL-22 and IL-27 in the assessment of microangiopathy and prognosis was evaluated through receiver operating characteristic (ROC) curve analysis. Results: Compared to the control group, the observation group exhibited significantly higher serum levels of fasting blood glucose, glycated hemoglobin, total cholesterol, triglycerides, low-density lipoprotein, uric acid, blood creatinine, cystatin C, IL-22 and IL-27, but lower glomerular filtration rate (all P<0.05). There were significant differences among different albuminuria groups in terms of duration of disease, serum levels of fasting blood glucose, low-density lipoprotein, cystatin C, IL-22, IL-27, and glomerular filtration rate (all P<0.05). Correlation analysis showed that the serum levels of IL-22 and IL-27 were positively correlated with the duration of disease and serum levels of fasting blood glucose, low-density lipoprotein, uric acid, blood creatinine and cystatin C. However, they were negatively correlated with glomerular filtration rate (P<0.05). The logistic regression analysis indicated that the glomerular filtration rate and serum levels of cystatin C, IL-22, and IL-27 were independent risk factors for the occurrence of microangiopathy. Compared to non-MACE group, the MACE group presented with higher serum IL-22 and IL-27 levels. ROC curve analysis showed that the AUC (Area Under the Curve) for combined detection (>0.9) of serum IL-22 and IL-27 levels was higher than that (>0.8) for each alone in assessing microangiopathy in DN patients. Additionally, the AUC for using serum IL-22 and IL-27 levels, whether individually or in combination, exceeded 0.7 when evaluating patient prognosis. Conclusion: Elevated serum IL-22 and IL-27 levels are closely associated with the severity of the DN and can serve as auxiliary indicators for assessing microangiopathy and prognosis in DN patients.

Keywords: Diabetic nephropathy, interleukin 22, interleukin 27, vasculopathy

Introduction

Diabetic nephropathy (DN) is the primary cause of end-stage renal disease, and epidemiological data show that 30%-40% of diabetic patients in China develop DN [1-5]. Clinically, early screening for DN is commonly performed through microalbuminuria detection [6, 7]. However, the accuracy of urine microalbumin detection can be easily affected by various fac-

tors, resulting in reduced sensitivity and specificity. Therefore, exploring effective biomarkers for assessing microangiopathy in DN patients holds significant clinical importance [8, 9]. Interleukin-27 (IL-27) is an inflammatory factor belonging to the Interleukin-12 (IL-12) family, known for its dual pro- and anti-inflammatory effects. On the one hand, IL-27 participates in inflammatory responses by inducing the differentiation of T cells into Th1 cells, which promote

the secretion of interferon-γ; on the other hand, IL-27 can inhibit the expression of IL-17 and enhance the production of IL-10, thus exerting anti-inflammatory effects [10]. Interleukin-22 (IL-22), secreted by Th22 cells, plays an important role in inflammation and immune regulation [11]. Currently, there is limited research on the roles of IL-22 and IL-27 in the microangiopathy associated with DN. This study explores the correlation between serum IL-22 and IL-27 levels and microangiopathy in DN patients, aiming to provide a basis for clinical diagnosis and treatment.

Patients and methods

General information

From January 2022 to December 2023, 104 DN patients treated at Shanxi University of Traditional Chinese Medicine Affiliated Hospital were selected as the observation group in this retrospective study. The inclusion criteria for the observation group were as follows: (1) All patients diagnosed with DN either by renal biopsy or based on clinical characteristics, including a glomerular filtration rate of <60 mL·min^{-1}·1.73 m^{-2}, continuous proteinuria of ≥30 mg over 24 hours, or both [12]; (2) Type 2 diabetes; (3) Age ≥18 years.

The exclusion criteria for the observation group were as follows: (1) Type 1 diabetes or other types of diabetes; (2) Pregnancy or lactation; (3) Presence of acute diabetic complications; (4) Coexisting kidney diseases; (5) Coexisting diseases affecting other tissues or organs; (6) Neurological or psychiatric disorders; (7) Poor compliance.

Another 104 healthy people from the same period were selected as a control group. Inclusion criteria for the control group: (1) Healthy physical examination within the last 3 months; (2) Age ≥18 years. Exclusion criteria: (1) Patients in pregnancy or in lactation; (2) Patients with a family history of diabetes. This study was approved by the Ethics Committee of Shanxi University of Traditional Chinese Medicine Affiliated Hospital.

The observation group was further divided into three subgroups based on urinary albumin excretion rate (UAER) [13]: clinical albuminuria group (UAER ≥300 mg/24 h, also microangiop-athy, 29 patients), microalbuminuria group (30 mg/24 h ≤ UAER <300 mg/24 h, 51 patients), and normal albuminuria group (UAER <30 mg/24 h, 24 patients).

Observation indicators

Clinical data were collected from all study subjects. A fasting venous blood sample of 5 ml was drawn from each patient in the early morning following enrollment. The blood was centrifuged at 3,000 r/min for 15 minutes to separate the serum. Serum levels of IL-22 and IL-27 were measured using an enzyme-linked immunosorbent assay (RT-6100 multifunctional microplate reader, Hamilton Company, Switzerland). All reagent kits were purchased from Shanghai Enzyme-linked Biotechnology Co., Ltd.

Follow up

The observation group was followed up by telephone and outpatient visit for 6 months. The endpoint event was major adverse cardiovascular events (MACE), which was defined as nonfatal myocardial infarction, nonfatal stroke, or deterioration of cardiac function. The DN patients were divided into a MACE group (n = 39) and a non-MACE group (n = 65) according to the occurrence of MACE.

Statistical methods

Data analysis was performed using SPSS 22.0. Quantitative data were presented as mean ± standard deviation ($\bar{x} \pm s$). Multiple group comparisons were conducted using analysis of variance, with pairwise comparisons between groups performed using LSD-t test. Categorical data were presented as percentages (%) and compared using the chi-square test. Multifactor analysis was conducted using logistic regression. Correlation analysis was performed using Pearson's method. Receiver Operating Characteristic (ROC) curves were plotted. A *P*-value of <0.05 was considered significant.

Results

Comparison of general data between the two groups

There were significant differences between the groups in terms of serum levels of fasting blood

Table 1. Comparison of general information between the two groups

Index	Observation group (n = 104)	Control group (n = 104)	χ^2/t	P
Age (years)	54.2±4.9	53.0±6.1	1.564	0.119
Sex				
Male	59	53	0.696	0.404
Female	45	51		
Body mass index (kg/m^2)	22.78±2.24	22.34±1.51	1.661	0.098
Systolic pressure (mmHg)	119.28±9.67	117.12±10.15	1.571	0.118
Diastolic blood pressure (mmHg)	79.15±8.22	78.26±8.78	0.755	0.451
Fasting blood glucose (mmol/L)	9.53±1.59	5.24±0.47	26.387	<0.001
Glycosylated hemoglobin (%)	7.47±0.72	5.28±0.39	27.275	<0.001
Total cholesterol (mmol/L)	5.63±0.71	4.74±0.58	9.900	<0.001
Triglyceride (mmol/L)	1.32±0.39	1.07±0.41	4.506	<0.001
Low density lipoprotein (mmol/L)	3.53±0.55	2.79±0.52	9.970	<0.001
Uric acid (umol/L)	473.16±82.31	224.57±35.23	28.315	<0.001
Serum creatinine (µmol/L)	146.48±39.56	85.22±19.27	14.197	<0.001
Glomerular filtration rate (ml/min/1.73 m^2)	98.52±8.17	109.44±12.54	7.441	<0.001
Cystatin C (mg/L)	1.37±0.39	0.65±0.21	16.577	<0.001
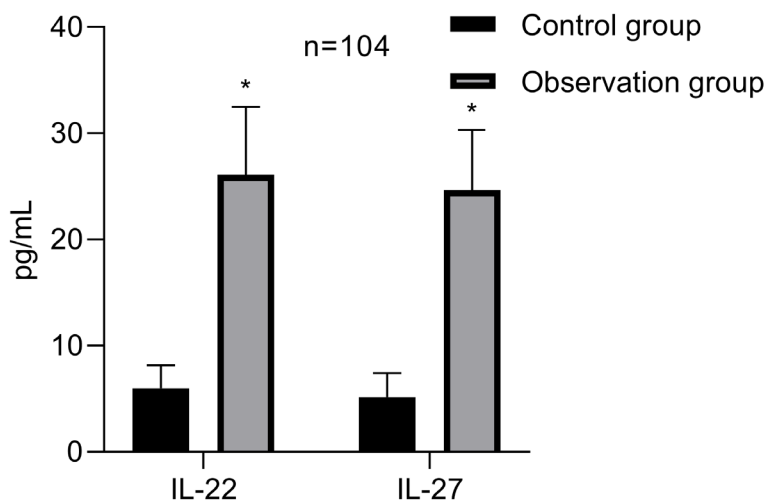
Figure 1. Comparison of IL-22 and IL-27 levels between the two groups. Note: *compared to the control group, P<0.05. IL-22, Interleukin-22; IL-27, interleukin-27.

respectively, while the IL-27 levels were 24.64±5.69 (pg/mL) and 5.16±2.24 (pg/mL) respectively. The differences between the two groups were significant (t = 30.526, 32.487; both P<0.001), as shown in **Figure 1**.

Comparison of various indicators among the different albuminuria groups

There were significant differences among the different albuminuria groups in terms of duration of disease, fasting blood glucose, low-density lipoprotein, uric acid, blood creatinine, cystatin C, IL-22, IL-27 levels, and glomerular filtration rate (all P<0.05), as shown in **Table 2**.

Correlation analysis

Correlation analysis showed that in DN patients, levels of IL-22 and IL-27 were positively correlated with the duration of the disease, fasting blood glucose, low-density lipoprotein, uric acid, blood creatinine, and cystatin C levels, but negatively correlated with glomerular filtration rate (all P<0.05), as shown in **Table 3**.

glucose, glycated hemoglobin, total cholesterol, triglycerides, low-density lipoprotein, uric acid, blood creatinine and cystatin C and glomerular filtration rate (all P<0.05), as shown in **Table 1**.

Comparison of IL-22 and IL-27 levels between the two groups

The results showed that the IL-22 levels in the observation group and control group were 26.09±6.39 (pg/mL) and 5.98±2.17 (pg/mL)

Table 2. Comparison of indicators among different urinary protein groups

Index	Clinical proteinuria group (n = 29)	Microalbuminuria group (n = 51)	Normal proteinuria group (n = 24)	F	P
Age (years)	54.6±3.1	54.1±3.0	53.7±3.4	0.557	0.575
Sex					
Male	17	27	15	0.666	0.717
Female	12	24	9		
Body mass index (kg/m²)	22.95±1.31	22.98±1.97	22.13±2.28	1.818	0.168
Duration of disease (years)	12.23±2.31[a,b]	10.04±2.07[a]	7.55±3.20	24.253	<0.001
Systolic pressure (mmHg)	120.44±7.71	118.29±8.75	119.97±7.82	0.735	0.482
Diastolic blood pressure (mmHg)	79.56±6.43	78.94±6.83	79.10±7.26	0.077	0.926
Fasting blood glucose (mmol/L)	10.42±1.01[a,b]	9.36±0.75[a]	8.81±0.62	38.820	<0.001
Glycosylated hemoglobin (%)	7.47±0.61	7.50±0.52	7.41±0.59	0.209	0.818
Total cholesterol (mmol/L)	5.70±0.64	5.58±0.69	5.62±0.65	0.299	0.742
Triglyceride (mmol/L)	1.37±0.37	1.30±0.31	1.30±0.29	0.489	0.614
Low density lipoprotein (mmol/L)	3.68±0.27[a,b]	3.51±0.20[a]	3.39±0.21	11.420	<0.001
Uric acid (umol/L)	496.28±48.59[a,b]	472.40±64.27[a]	446.86±32.28	5.470	0.006
Serum creatinine (μmol/L)	163.12±14.25[a,b]	145.28±31.90[a]	128.92±15.47	12.614	<0.001
Glomerular filtration rate (ml/min/1.73 m²)	95.92±3.41[a,b]	97.23±3.74[a]	104.40±3.92	40.692	<0.001
Cystatin C (mg/L)	1.62±0.24[a,b]	1.34±0.21[a]	1.13±0.15	37.750	<0.001
IL-22 (pg/mL)	32.16±4.92	24.70±4.69	21.71±5.90	31.877	<0.001
IL-27 (pg/mL)	28.58±5.01	24.74±4.08	22.54±4.21	13.278	<0.001

Note: [a]compared to normal proteinuria group, P<0.05; [b]compared to microproteinuria group, P<0.05. IL-22, Interleukin-22; IL-27, interleukin-27.

Table 3. Results of correlation analysis

Index	IL-22 (pg/mL)		IL-27 (pg/mL)	
	r	P	r	P
Duration of disease (years)	0.429	<0.001	0.378	0.037
Fasting blood glucose (mmol/L)	0.441	<0.001	0.416	<0.001
Low density lipoprotein (mmol/L)	0.398	0.011	0.412	0.015
Uric acid (μmol/L)	0.415	0.003	0.398	<0.001
Serum creatinine (μmol/L)	0.442	<0.001	0.425	0.002
Glomerular filtration rate (ml/min/1.73 m²)	-0.395	0.005	-0.376	0.022
Cystatin C (mg/L)	0.404	<0.001	0.388	0.029

IL-22, Interleukin-22; IL-27, interleukin-27.

Table 4. Assignment table

Index	Assignment
Duration of disease (years)	≥12.23 = 1; <12.23 = 0
Fasting blood glucose (mmol/L)	≥10.42 = 1; <10.42 = 0
Low density lipoprotein (mmol/L)	≥3.68 = 1; <3.68 = 0
Uric acid (μmol/L)	≥496.28 = 1; <496.28 = 0
Serum creatinine (μmol/L)	≥163.12 = 1; <163.12 = 0
Glomerular filtration rate (ml/min/1.73 m²)	≥95.92 = 1; >95.92 = 0
Cystatin C (mg/L)	≥1.62 = 1; <1.62 = 0
IL-22 (pg/mL)	≥32.16 = 1; <32.16 = 0
IL-27 (pg/mL)	≥28.58 = 1; <28.58 = 0

IL-22, Interleukin-22; IL-27, interleukin-27.

Logistic regression analysis

Variables that showed statistical significance in the univariate analysis were assigned values, as shown in **Table 4**. The results of the multivariate logistic regression analysis indicated that glomerular filtration rate, cystatin C, IL-22, and IL-27 levels were independent risk factors for the occurrence of microangiopathy, as shown in **Table 5**.

Table 5. Logistic regression analysis results

Index	β	SE	Wald	OR	95% CI	P
Glomerular filtration rate (ml/min/1.73 m²)	1.550	0.492	9.925	4.71	3.10-6.84	<0.001
Cystatin C (mg/L)	2.115	0.617	11.750	8.29	3.98-25.26	<0.001
IL-22 (pg/mL)	0.820	0.295	7.727	2.27	1.87-5.09	<0.001
IL-27 (pg/mL)	0.445	0.216	4.244	1.56	1.16-4.25	0.019

IL-22, Interleukin-22; IL-27, interleukin-27.

Table 6. ROC curve results

Variable	Cut-off value	AUC	95% CI	Sensitivity	Specificity	P
IL-22 (pg/mL)	30.65	0.84	0.75, 0.92	0.83	0.85	<0.001
IL-27 (pg/mL)	24.50	0.78	0.68, 0.88	0.76	0.75	<0.001
Joint assessment	-	0.95	0.84, 0.97	0.90	0.84	<0.001

IL-22, Interleukin-22; IL-27, interleukin-27.
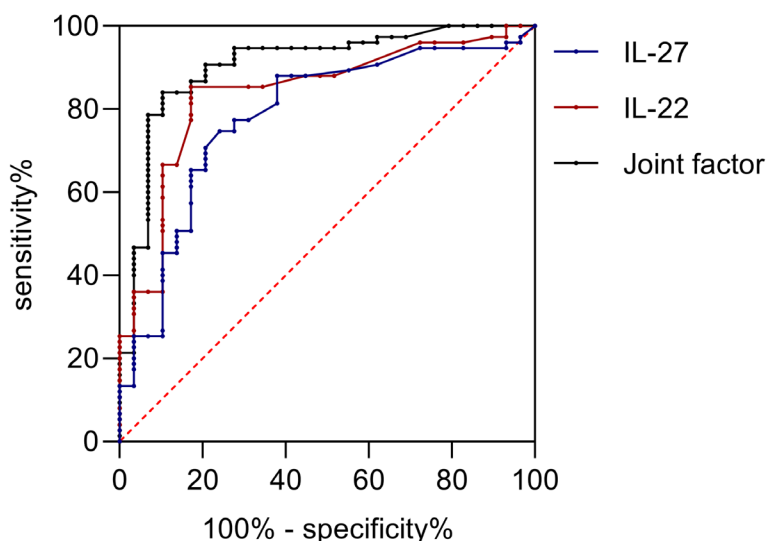
Figure 2. ROC curve. IL-22, Interleukin-22; IL-27, interleukin-27.

Clinical value of IL-22 and IL-27 in the assessment of microangiopathy

The ROC curve analysis showed that IL-22 or IL-27 for assessing patients' microangiopathy yielded an Area Under the Curve (AUC) greater than 0.80. Notably, combined testing resulted in an AUC greater than 0.90, as shown in **Table 6** and **Figure 2**.

Comparison of IL-22 and IL-27 levels between MACE and non-MACE groups

The results of comparing IL-22 and IL-27 levels between MACE and non-MACE groups showed that both IL-22 and IL-27 levels were higher in the MACE group compared to the non-MACE group (all P<0.05), as shown in **Table 7**.

Clinical value of IL-22 and IL-27 levels in assessing patient prognosis

The results showed that both IL-22 and IL-27, alone or in combination, had an AUC of >0.7 for assessing the prognosis of the patients, as shown in **Table 8** and **Figure 3**.

Discussion

Early detection of vasculopathy in patients with diabetic nephropathy (DN) and timely intervention are of great clinical importance. Urinary albumin, as one of the biomarkers of endothelial dysfunction, has been widely used for the early diagnosis of DN [14, 15]. This study found that compared to the normal population, patients with DN have increased glucose and lipids. In addition, there were significant differences between DN patients and the normal population in terms of uric acid, blood creatinine, glomerular filtration rate, and cystatin C, aligning with previous research findings [16]. However, these indicators have limitations, such as low specificity and sensitivity for diagnosing DN. Therefore, identifying effective biomarkers for assessing the condition of DN and timely predicting vasculopathy is of significant clinical importance.

Table 7. Comparison of IL-22 and IL-27 levels between MACE group and non-MACE group

Index	MACE group (n = 39)	Non-MACE group (n = 65)	t	P
IL-22 (pg/mL)	29.19±6.02	24.23±5.90	4.116	<0.001
IL-27 (pg/mL)	27.11±5.49	23.16±5.32	3.623	<0.001

MACE, major adverse cardiovascular events; IL-22, Interleukin-22; IL-27, interleukin-27.

Table 8. The clinical value of IL-22 and IL-27 levels in evaluating the prognosis of patients

Variable	Cut-off value	AUC	95% CI	Sensitivity	Specificity	P
IL-22 (pg/mL)	23.89	0.72	0.62, 0.82	0.74	0.66	<0.001
IL-27 (pg/mL)	23.95	0.70	0.59, 0.81	0.69	0.72	<0.001
Joint factor	-	0.77	0.67, 0.87	0.54	0.92	<0.001

IL-22, Interleukin-22; IL-27, interleukin-27.
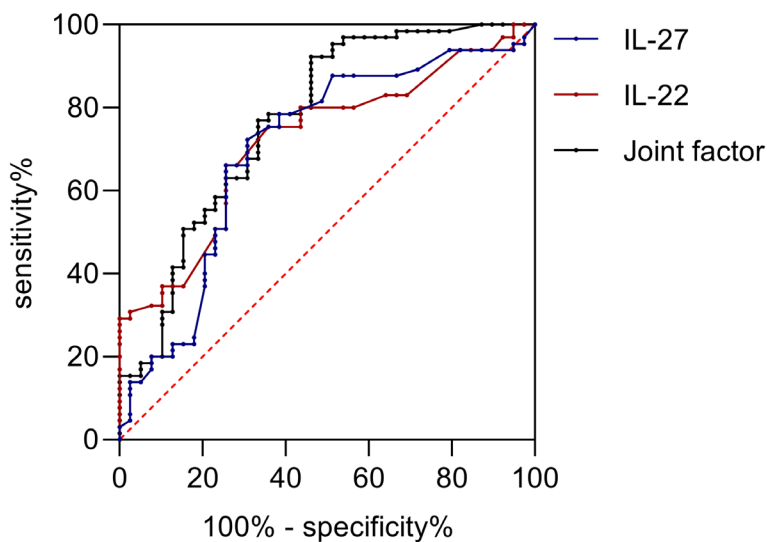
Figure 3. ROC curve of IL-22 and IL-27 levels in assessing patient prognosis. IL-22, Interleukin-22; IL-27, interleukin-27.

Current research suggests that body-related inflammatory factors can serve as potential targets for the diagnosis and treatment of DN [17]. IL-27 has both anti- and pro-inflammatory effects; it promotes the differentiation of CD4+ T cells towards Th1 and stimulates the expression of inflammatory cytokines such as IL-6 and IL-12 in monocytes [18, 19]. Studies have found that Th1 is closely related to the level of urinary protein in diabetic patients, yet there is limited research on IL-27 expression levels in DN patients [20]. The results of this study show that compared to the normal population, IL-27 levels were significantly elevated in patients with DN, and they increased along with urinary protein levels. This suggests that IL-27 expression is associated with the progression of DN. The possible mechanism is that IL-27 may con-

tribute to the progression of DN by disrupting the balance of Th1/Th2 cell ratios, promoting the secretion of inflammatory factors, leading to growth and proliferation of glomerular mesangial cells, thickening of the extracellular matrix, and expansion of the mesangial areas, thereby worsening the condition of DN.

IL-22 is a member of the IL-10 family, primarily secreted by Th22 cells, and plays a role in the development and progression of several inflammatory diseases [21, 22]. On the one hand, IL-22 can protect the host by being highly expressed in response to external threats. On the other hand, excessive secretion of IL-22, influenced by the local cellular cytokine environment, can cause damage to the body. Previous research has observed increased IL-22 expression in conditions such as rheumatoid arthritis and psoriasis [23, 24]. However, reports on its role in kidney diseases are still scarce.

The results of this study indicate that IL-22 levels are also elevated in patients with DN. Furthermore, this study divided DN patients into different subgroups based on their levels of proteinuria for further analysis. The results showed that as proteinuria levels increase, patients exhibit higher fasting blood glucose, low-density lipoprotein, cystatin C, IL-22, and IL-27 levels, while their glomerular filtration

rates decreased. This suggests that higher proteinuria levels are indicative of more severe disease progression [25]. Additionally, the study also found that IL-22 and IL-27 levels in DN patients were closely related to disease duration, fasting blood glucose, low-density lipoprotein, cystatin C levels, and glomerular filtration rates, further confirming that IL-22 and IL-27 are involved in the process of microvascular disease in DN patients and are closely related to the severity of the condition.

The results of the logistic regression analysis showed that glomerular filtration rate, cystatin C, IL-22, and IL-27 were independent risk factors for the occurrence of microangiopathy. This indicates that in clinical practice, patients with high levels of cystatin C, high expression of IL-22 and IL-27, and low glomerular filtration rates should be closely monitored, and timely interventions should be taken to prevent further progression of the disease.

The study further investigated the clinical value of IL-22 and IL-27 in assessing microangiopathy as well as in evaluating the prognosis of patients. The findings revealed that IL-22 and IL-27 levels were significantly higher in patients with MACE compared to those without MACE. In addition, the AUCs of IL-22 and IL-27 alone in assessing microangiopathy were both greater than 0.7, and the AUC of the combine test exceeded 0.9, suggesting that the combined test of the two has higher clinical value in assessing microangiopathy. Furthermore, the AUC of IL-22 and IL-27, whether measured individually or in combination, was greater than 0.7 for assessing patient prognosis. This provides a new perspective for evaluating the prognosis of patients with DN.

However, this study has limitations, including the fact that the sample was from a single center, resulting in a relatively small sample size. Furthermore, the differences in the levels of IL-22 and IL-27 in patients with different diabetic complications were not further analyzed, making it difficult to analyze the specificity of the indexes.

In summary, the levels of IL-22 and IL-27 are elevated in patients with DN and are closely related to the severity of the disease. They can be used as auxiliary indicators for assessing microangiopathy and prognosis in DN patients.

Disclosure of conflict of interest

None.

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