Research Square

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A Clinical Study on Biomarkers Affecting the Prognosis of Anti-VEGF Treatment in Diabetic Macular Edema

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Abstract

Objective

This study aimed to investigate prognostic biomarkers associated with the heterogeneous response to anti-VEGF therapy in patients with diabetic macular edema (DME) using multimodal data analysis, including aqueous humor cytokines, peripheral blood inflammatory markers, lipid profiles, renal function indicators and optical coherence tomography (OCT) features, so as to provide evidence for individualized treatment.

Methods

In this retrospective cohort study, DME patients treated with anti-VEGF between April 2023 and May 2024 were enrolled and categorized into good responders (central macular thickness [CMT]reduction ≥ 25%) and poor responders (CMT reduction < 25%), with non-diabetic cataract patients as controls. Analyzed parameters included aqueous humor factors (VEGF, ICAM-1, MCP-1, IP-10, IL-6, IL-8), peripheral blood indices (neutrophil-to-lymphocyte ratio [NLR], systemic immune-inflammation index[SII], systemic inflammation response index [SIRI]), lipid profiles, renal function markers, and OCT biomarkers. Statistical analyses involved univariate analysis, Spearman correlation, and receiver operating characteristic (ROC) curve analysis ($P < 0.05$).

Results

DME patients had significantly higher aqueous levels of VEGF,ICAM-1, IL-6, and IL-8 than controls($P < 0.05$).Poor responders exhibited lower VEGF levels but higher IP-10, IL-8, SII, SIRI, total cholesterol (TC), and cystatin C (Cys-C) levels ($P < 0.05$).Baseline CMT was lower in poor responders, while hyperreflective foci(HRF), disorganization of retinal inner layers (DRIL),and vitreomacular interface abnormalities (VIMA) were more frequent ($P < 0.05$). ROC analysis identified VEGF, IP-10, IL-8, SII, SIRI, TC, Cys-C, CMT, HRF, DRIL, and VIMA as predictive biomarkers.

Conclusion

Aqueous humor cytokines, systemic inflammatory indices, lipid parameters, renal function markers, baseline CMT, and OCT biomarkers are potential predictors for anti-VEGF treatment response in DME, emphasizing the role of inflammation and systemic factors in therapeutic outcomes and supporting the development of personalized strategies

1. Introduction

Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia, which can lead to multi-organ damage, with ocular complications being particularly prominent. Diabetic retinopathy (DR), a critical microvascular complication of diabetes, has emerged as the leading cause of vision loss among working-age adults. Epidemiological data indicate that approximately one-third of diabetic patients develop DR, with a marked increase in incidence after the age of 60[1]. DME, a severe manifestation of DR, involves pathophysiological mechanisms such as disruption of the inner blood-retinal barrier, enhanced vascular permeability, and inflammatory cytokine cascades, ultimately resulting in fluid accumulation in the macular region. Global burden studies report a significant rise in DME prevalence, projected to increase by 51.9% by 2045[2], thereby amplifying its adverse effects on visual quality and socioeconomic outcomes and underscoring the need for effective diagnostic and therapeutic strategies.

Current management of DME primarily encompasses systemic risk factor control, intravitreal anti-VEGF therapy, retinal laser photocoagulation, and pars plana vitrectomy (PPV). International guidelines consistently recommend intravitreal anti-VEGF agents as the first-line treatment, owing to their efficacy in suppressing VEGF-mediated vascular leakage and

neovascularization, while partially restoring blood-retinal barrier integrity. However, a substantial proportion of patients exhibit suboptimal responses to anti-VEGF therapy in clinical practice. Evidence from clinical studies demonstrates that 31.6% to 65.6% of patients undergoing standard regimens (e.g., ≥ 4 injections within 24 weeks) display treatment resistance[3]. These observations highlight the imperative for pre-therapeutic biomarker-based prognostic evaluation to advance precision medicine in DME, enabling tailored therapeutic strategies for distinct patient phenotypes.

2. Methods

This study was approved by the Ethics Committee of the Second Hospital of Jilin University and strictly adhered to the principles of the “Declaration of Helsinki”. All patients were informed and signed informed consent form. Patients with DME who first visited the Ophthalmology Outpatient Department of the Second Hospital of Jilin University from April 2023 to May 2024 and received the 3 + PRN anti-VEGF treatment regimen (2 mg/0.05 mL Aflibercept intravitreal injection) were collected as the DME group. The DME group was divided into the following 2 groups based on the magnitude of CMT reduction after 3 months of anti-VEGF drug treatment: Good response group: CMT reduction ≥ 25% (16 patients, 19 eyes). Poor response group: CMT reduction < 25% (18 patients, 20 eyes). At the same time, patients with age-related cataracts undergoing cataract extraction surgery who denied a history of diabetes mellitus in our hospital were collected as the control group(8 patients, 8 eyes). All data of patients who met the inclusion criteria were analyzed.

Baseline information was collected on all patients. General information: age, sex, fasting plasma glucose (FPG), glycosylated haemoglobin (HbA1c). Systemic biomarkers: routine blood test, lipid profiles (TC, TG, HDL, LDL etc.), renal function markers (cystatin-C, eGFR etc.). Based on the above measurements, new peripheral blood inflammation indicators were calculated using the following formulas: NLR = Absolute neutrophil count / Absolute lymphocyte count; SII = Absolute neutrophil count * Platelet count / Absolute lymphocyte count; SIRI = Absolute neutrophil count * Absolute monocyte count / Absolute lymphocyte count; dNLR = Absolute neutrophil count / (White blood cell count - Absolute neutrophil count); MPVLR = Mean platelet volume / Absolute lymphocyte count; M/GLR = (White blood cell count - Absolute lymphocyte count) / Absolute lymphocyte count. OCT parameters: baseline CMT, intraretinal cysts (IRC), hyperreflective foci (HRF), disorganization of retinal inner layers (DRIL), external limiting membrane/ellipsoid zone (ELM/EZ) integrity, subretinal fluid (SRF), vitreomacular interface abnormalities (VIMA). Aqueous humor cytokines: All patients had 50 μL of aqueous humor drawn before surgery, and the collected aqueous humor samples were immediately placed in sterile EP tubes and stored in a -80°C freezer for testing. Baseline concentrations of VEGF, ICAM-1, MCP-1, IP-10, IL-6, and IL-8 in aqueous humor were measured by Cytometric Bead Array (CBA) technique.

All data were collected and organized using Microsoft Excel. Detailed statistical analysis of the collected data was performed using IBM SPSS 27.0 and GraphPad Prism 9.5.1 statistical software. Continuous variables were compared using independent t-tests (normal distribution) or Wilcoxon rank-sum tests (non-normal). Categorical variables were analyzed with chi-square or Fisher’s exact tests. Spearman rank correlation test was used for correlation analysis. ROC curves were used to evaluate the predictive value of each biomarker. $P<0.05$ indicated statistically significant differences.

3. Results

3.1 Comparative Analysis of General Data

A total of 8 patients (8 eyes) met the inclusion criteria for the control group. The DME cohort was stratified into two subgroups: 16 patients (19 eyes) in the good response group and 18 patients (20 eyes) in the poor response group.

General data and clinical characteristics analyzed included age, sex, eye laterality, fasting plasma glucose (FPG), and glycated hemoglobin (HbA1c) levels. Baseline parameters were as follows:

Control group: 8 patients (3 males [37.5%], 5 females [62.5%]; mean age 57.00 ± 4.14 years)

Good response group: 16 patients (8 males [50.0%], 8 females [50.0%]; mean age 56.81 ± 10.73 years; FPG 9.13 ± 3.17 mmol/L; HbA1c 7.21% ± 1.50)

Poor response group: 18 patients (13 males [72.2%], 5 females [27.8%]; mean age 54.50 ± 9.62 years; FPG 9.05 ± 2.75 mmol/L; HbA1c 7.53% ± 1.72)

As detailed in Table 1, no statistically significant differences were observed between the DME cohort and controls regarding age (P = 0.538), sex distribution (P = 0.395), or eye laterality (P = 0.747). Similarly, comparative analyses revealed no significant differences in age (P = 0.51P = 0.51), sex (P = 0.15,P = 0.15), ocular laterality (P = 0.77,P = 0.77), FPG (P = 0.92,P = 0.92), or HbA1c (P = 0.57,P = 0.57) between the good and poor response groups.

Table 1
General Data Comparison of Study Subjects

	Control Group	**DME Group**		***P* Value**	
	(*n* = 8)	**Good Response Group (*n* = 16)**	**Poor Response Group (*n* = 18)**	**Control Group and DME Group**	**Good Response Group and Poor Response Group**
Age (years)	57.004.14	56.8110.73	54.509.62	0.538	0.512
sex (n, %)				0.395	0.291
Male	3(37.50)	8(50.00)	13(72.20)		
Female	5(62.50)	8(50.00)	5(27.8)		
Eye laterality (N, %)				0.747	0.562
N	8	19	20		
Left eye	3(37.50)	10(52.60)	10(50.00)		
Right eye	5(62.50)	9(47.40)	10(50.00)		
FPG (mmol/L)	-	9.133.17	9.052.75	-	0.938
HbA1c (%)	-	7.211.50	7.531.72	-	0.566
Note: *P* < 0.05 indicated statistically significant differences					

3.2 Comparative Analysis of Aqueous Humor Cytokine Profiles

The analyzed cytokines included VEGF, intercellular adhesion molecule-1 (ICAM-1), monocyte chemoattractant protein-1 (MCP-1), interferon gamma-induced protein-10 (IP-10), interleukin-6 (IL-6), and interleukin-8 (IL-8).

The median concentrations of each factor were as follows:

Control group :VEGF:3.40 (0.75, 6.01) pg/mL; ICAM-1:305.60 (237.83, 445.48) pg/mL; MCP-1:473.51 (337.99, 536.23) pg/mL; IP-10 : 26.66 (10.80, 40.02) pg/mL; IL-6 : 6.84 (1.97, 18.74) pg/mL; IL-8 : 0.61 (0, 2.57) pg/mL. DME group: VEGF :10.48 (2.77, 49.13) pg/mL; ICAM-1 : 1399.20 (882.65, 1733.04) pg/mL; MCP-1: 557.16 (396.33, 750.32) pg/mL; IP-10 : 49.34 (20.29, 80.24) pg/mL; IL-6 : 28.34 (13.48, 100.69) pg/mL; IL-8 : 12.64 (8.31, 20.86) pg/mL.

The statistical results of Table 2 and Fig. 1 indicated that the concentrations of VEGF, ICAM-1, IL-6, and IL-8 in the aqueous humor of patients in the DME group were higher than those in the control group, with statistically significant differences (*P* =

0.019, < 0.001, 0.017, and < 0.001, respectively); the concentrations of MCP-1 and IP-10 were also higher than those in the control group, but the differences were not statistically significant ($P > 0.05$).

Table 2
Comparison of Baseline Concentrations of Aqueous Humor Cytokines Between Control Group and DME Group

VEGF(pg/mL)	**Control Group (*n* = 8)**	**DME Group (*n* = 39)**	***P* Value**
	3.40(0.75,6.01)	**10.48(2.77,49.13)**	**0.019[&]**
ICAM-1(pg/mL)	305.60(237.83,445.48)	1399.20(882.65,1733.04)	**<0.001[&]**
MCP-1(pg/mL)	473.51(337.99,536.23)	557.16(396.33,750.32)	0.111
IP-10(pg/mL)	26.66(10.80,40.02)	49.34(20.29,80.24)	0.067
IL-6(pg/mL)	6.84(1.97,18.74)	28.34(13.48,100.69)	**0.017[&]**
IL-8(pg/mL)	0.61 (0,2.57)	12.64(8.31,20.86)	**<0.001[&]**
Note: [&]Wilcoxon rank-sum test			
[&]*P* < 0.05 indicated statistically significant differences			

Good response group: VEGF :22.7 (10.48, 53.73) pg/mL, ICAM-1 : 1265.59±627.64 pg/mL, MCP-1 :497.88 (384.24, 661.76) pg/mL, IP-10 : 42.69 (14.32, 66.09) pg/mL, IL-6 : 24.62 (11.21, 84.00) pg/mL, IL-8 :12.04 (5.20, 16.98) pg/mL. Poor response group:VEGF : 6.72 (1.70, 18.31) pg/mL, ICAM-1:1658.47±931.68 pg/mL,MCP-1 : 602.23 (468.23, 1166.65) pg/mL, IP-10:62.95 (37.48, 135.90) pg/mL, IL-6 : 34.75 (14.26, 148.73) pg/mL, IL-8 : 19.48 (10.95, 49.13) pg/mL.

The statistical results of Table 3 and Fig. 2 showed that the concentration of VEGF in the aqueous humor of patients in the poor response group was lower than that in the good response group, and the difference was statistically significant ($P < 0.05$); the concentrations of IP-10 and IL-8 were higher than those in the good response group, and the differences were statistically significant ($P = 0.033$ and 0.025, respectively); the concentrations of ICAM-1, MCP-1, and IL-6 were higher than those in the good response group, but the differences were not statistically significant ($P>0.05$).

Table 3
Comparison of Baseline Concentrations of Cytokines in Aqueous Humor Between Good Response Group and Poor Response Group

VEGF(pg/mL)	Good Response Group (*n* = 19)	Poor Response Group (*n* = 20)	*P* Value
	22.7(10.48,53.73)	**6.72(1.70,18.31)**	**0.043&**
ICAM-1(pg/mL)	1265.59627.64	1658.47931.68	0.133
MCP-1(pg/mL)	497.88(384.24,661.76)	602.23(468.23,1166.65)	0.196
IP-10(pg/mL)	42.69(14.32,66.09)	62.95(37.48,135.90)	**0.033&**
IL-6(pg/mL)	24.62(11.21,84.00)	34.75(14.26,148.73)	0.473
IL-8(pg/mL)	12.04(5.20,16.98)	19.48(10.95,49.13)	**0.025&**
Note: &Wilcoxon rank-sum test			
&*P* < 0.05 indicated statistically significant differences			

3.3 Comparative Analysis of Peripheral Blood Inflammatory Indicators

Control group: There were 8 patients, among whom the mean WBC was (6.04 ± 2.16)*10^9/L, the mean Neut was (3.49 ± 1.48)*10^9/L, the mean Lymph was [1.86 (1.35,1.98)]*10^9/L, the mean Mono was [0.39 (0.28,0.55)]*10^9/L, the mean RDWCV was (12.74 ± 0.67)%, the mean NLR was 1.97 ± 0.83, the mean SII was 321.46 (267.73,689.97), the mean SIRI was 0.61 (0.45,1.35), the mean dNLR was 1.46 ± 0.55, the mean MPVLR was 5.69 ± 2.63, and the mean M/GLR was 2.30 ± 0.89. DME group: There were 34 patients, among whom the mean WBC was (7.19 ± 1.82)*10^9/L, the mean Neut was (4.80 ± 1.44)*10^9/L, the mean Lymph was [1.80 (1.50,1.90)]*10^9/L, the mean Mono was [0.40 (0.30,0.60)]*10^9/L, the mean RDWCV was (13.04 ± 0.59)%, the mean NLR was 2.92 ± 0.94, the mean SII was 559.09 (476.40,765.84), the mean SIRI was 1.16 (0.92,1.88), the mean dNLR was 2.08 ± 0.56, the mean MPVLR was 5.94 ± 1.47, and the mean M/GLR was 3.33 ± 1.07.

As shown in the intergroup analysis results of Table 4, Neut (*P* = 0.028), NLR (*P* = 0.013), SII (*P* = 0.048), SIRI (*P* = 0.017), dNLR (*P* = 0.009), and M/GLR (*P* = 0.017) showed statistical differences between the DME group and the control group, with levels in the DME group higher than those in the control group. The remaining peripheral blood inflammatory indicators showed no significant statistical differences (*P* > 0.05).

Table 4
Comparison of Peripheral Blood Inflammatory Indicators Between Control Group and DME Group

WBC(*10^9/L)	**Control Group (*n* = 8)**	**DME Group (*n* = 34)**	***P* Value**
	6.042.16	**7.191.82**	**0.135**
Neut(*10^9/L)	3.491.48	4.801.44	**0.028***
Lymph(*10^9/L)	1.86(1.35,1.98)	1.80(1.50,1.90)	0.421
Mono(*10^9/L)	0.39(0.28,0.55)	0.40(0.30,0.60)	0.483
RDWCV(%)	12.740.67	13.040.59	0.217
NLR	1.970.83	2.920.94	**0.013***
SII	321.46(267.73,689.97)	559.09(476.40,765.84)	**0.048&**
SIRI	0.61(0.45,1.35)	1.16(0.92,1.88)	**0.017&**
dNLR	1.460.55	2.080.56	**0.009***
MPVLR	5.692.63	5.941.47	0.722
M/GLR	2.300.89	3.331.07	**0.017***
Note: *Independent sample *t*-test			
&Wilcoxon rank-sum test			
*&*P* < 0.05 indicated statistically significant differences			

Good response group: There were 16 patients, among whom the mean WBC was (6.89 ± 1.76)*10^9/L, the mean Neut was [4.06 (3.34, 5.91)]*10^9/L, the mean Lymph was (1.82 ± 0.39)*10^9/L, the mean Mono was (0.38 ± 0.14)*10^9/L, the mean RDWCV was (12.84 ± 0.43)%, the mean NLR was 2.57 ± 0.91, the mean SII was 513.43 ± 213.87, the mean SIRI was 0.89 (0.52, 1.37), the mean dNLR was 1.96 ± 0.62, the mean MPVLR was 5.65 ± 1.60, and the mean M/GLR was 3.00 (2.13, 3.52). Poor response group: There were 18 patients, among whom the mean WBC was (7.43 ± 1.83)*10^9/L, the mean Neut was [4.78 (3.87, 5.78)]*10^9/L, the mean Lymph was (1.66 ± 0.36)*10^9/L, the mean Mono was (0.47 ± 0.13)*10^9/L, the mean RDWCV was (13.22 ± 0.63)%, the mean NLR was 3.11 ± 0.90, the mean SII was 707.37 ± 261.15, the mean SIRI was 1.31 (1.02, 1.88), the mean dNLR was 2.13 ± 0.49, the mean MPVLR was 6.02 ± 1.34, and the mean M/GLR was 3.39 (2.99, 3.75).

As shown in the intergroup analysis results of Table 5, the poor response group showed higher SII and SIRI than the good response group, and the results had statistical significance (*P* = 0.025 and 0.027, respectively); the other peripheral blood inflammatory indicators showed no significant statistical differences (*P* > 0.05).

Table 5
Comparison of Peripheral Blood Inflammatory Indicators Between Good Response Group and Poor Response Group

WBC(10^9/L)	**Good Response Group (*n* = 16)**	**Poor Response Group (*n* = 18)**	***P* Value**
	6.891.76	**7.431.83**	**0.391**
Neut(10^9/L)	4.06(3.34,5.91)	4.78(3.87,5.78)	0.334
Lymph(10^9/L)	1.820.39	1.660.36	0.218
Mono(10^9/L)	0.380.14	0.470.13	0.054
RDWCV(%)	12.840.43	13.220.63	0.051
NLR	2.570.91	3.110.90	0.089
SII	513.43213.87	707.37261.15	0.025*
SIRI	0.89(0.52,1.37)	1.31(1.02,1.88)	0.027&
dNLR	1.960.62	2.130.49	0.385
MPVLR	5.651.60	6.021.34	0.469
M/GLR	3.00(2.13,3.52)	3.39(2.99,3.75)	0.070
Note: *Independent sample *t*-test			
&Wilcoxon rank-sum test			
*□&*P* < 0.05 indicated statistically significant differences			

3.4 Comparative Analysis of Serum Lipid Profiles and Renal Function Parameters

The biochemical indicators included in the difference analysis of blood lipids and renal function were total cholesterol (TC), triglycerides (TG), high density lipoprotein (HDL), low density lipoprotein (LDL), blood uric acid (BUA), blood urea nitrogen (BUN), blood creatinine (Scr), glomerular filtration rate (eGFR), serum cystatin C (Cys-C), α1-microglobulin (α1-MG), and β2-microglobulin (β2-MG). Good response group: TC :4.72 ± 1.40 mmol/L, TG : 1.56 (1.09, 2.51) mmol/L, HDL: 1.23 ± 0.41 mmol/L, LDL: 2.12 (1.35, 3.71) mmol/L, BUA : 300.00 (255.25, 375.75) μmol/L, BUN : 7.34 (5.57, 7.87) mmol/L, Scr : 63.50 (52.25, 85) μmol/L, eGFR : 91.7 ± 20.09 mL/min, Cys-C : 0.79 (0.69, 1.00) mg/L, α1-MG : 20.01 (19.00, 25.80) mg/L, β2-MG : 1.72 (1.39, 2.29) mg/L. Poor response group: TC □ 5.64 ± 0.76 mmol/L, TG □ 1.90 (1.36, 3.09) mmol/L, HDL □ 1.23 ± 0.49 mmol/L, LDL □ 2.84 (2.22, 3.70) mmol/L, BUA □ 319.00 (272.75, 380.27) μmol/L, BUN □ 6.60 (4.43, 7.58) mmol/L, Scr □ 74.00 (58.75, 91.25) μmol/L, eGFR □ 82.38 ± 22.87 mL/min, Cys-C □ 1.05 (0.84, 1.75) mg/L, α1-MG □ 21.69 (20.06, 28.73) mg/L, β2-MG □2.02 (1.73, 2.43) mg/L.

As shown in Table 6, the TC and Cys-C levels in the poor response group were higher than those in the good response group, and the results had statistical significance (*P* = 0.028 and 0.035, respectively); there were no significant statistical differences in the other biochemical indicators (P > 0.05).

Table 6
Comparison of Biochemical Indicators Such as Blood Lipids and Renal Function Between Good Response Group and Poor Response Group

TC(mmol/L)	**Good Response Group (*n* = 16)**	**Poor Response Group (*n* = 18)**	***P* Value**
	4.721.40	**5.640.76**	**0.028***
TG(mmol/L)	1.56(1.09,2.51)	1.90(1.36,3.09)	0.173
HDL(mmol/L)	1.230.41	1.230.49	0.974
LDL(mmol/L)	2.12(1.35,3.71)	2.84(2.22,3.70)	0.196
BUA(μmol/L)	300.00(255.25,375.75)	319.00(272.75,380.27)	0.458
BUN(mmol/L)	7.34(5.57,7.87)	6.60(4.43,7.58)	0.292
Scr(μmol/L)	63.50(52.25,85)	74.00(58.75,91.25)	0.351
eGFR (ml/min)	91.720.09	82.3822.87	0.219
Cys-C(mg/L)	0.79(0.69,1.00)	1.05(0.84,1.75)	**0.035&**
α1-MG(mg/L)	20.01(19.00,25.80)	21.69(20.06,28.73)	0.269
β2-MG(mg/L)	1.72(1.39,2.29)	2.02(1.73,2.43)	0.202
Note: *Independent sample *t*-test			
&Wilcoxon rank-sum test			
*&*P* < 0.05 indicated statistically significant differences			

5. Difference Analysis of Baseline CMT and OCT Biomarkers Among Patient Groups

The baseline OCT imaging indicators included in the difference analysis were CMT, HRF, IRC, DRIL, interruption of ELM and/or EZ continuity, SRF, and VMIA.

As shown in Table 2.7, the mean baseline CMT was 483.00 (424.00, 598.00) μm in the good response group and 331.50 (287.50, 422.25) μm in the poor response group. Analysis using the Wilcoxon rank-sum test indicated that the baseline CMT in the poor response group was lower than that in the good response group, and the difference between the two groups was statistically significant ($P = 0.001$). The number of HRF, DRIL, and VMIA in the poor response group was significantly increased compared to the that of the good response group, with statistically significant differences ($P < 0.001$, 0.003, and 0.005, respectively). There were no statistically significant differences in the other OCT biomarkers ($P > 0.05$).

Table 2.7
Comparison of Baseline CMT and OCT Biomarkers Between Good Response Group and Poor Response Group

Baseline CMT (μm)	**Good Response Group (*n* = 19)**	**Poor Response Group (*n* = 20)**	***P* Value**
	483.00(424.00,598.00)	**331.50(287.50,422.25)**	**0.001[&]**
HRF(*n*,%)			
Present	5(26.30)	16(80.00)	**<0.001[#]**
Absent	14(73.70)	4(20.00)	
IRC(*n*,%)			
Present	19(100.00)	18(90.00)	0.256
Absent	0(0.00)	2(10.00)	
DRIL(*n*,%)			
Present	10(52.60)	19(95.00)	**0.003[#]**
Absent	9(47.40)	1(5.00)	
ELM and/or EZ Discontinuity (*n*,%)			
Present	14(73.70)	19(95.00)	0.080
Absent	5(26.30)	1(5.00)	
SRF(*n*,%)			
Present	7(36.80)	8(40.00)	0.550
Absent	12(63.20)	12(60.00)	
VMIA(*n*,%)			
Present	1(5.30)	9(45.00)	**0.005[#]**
Absent	18(94.70)	11(55.00)	
Note: [#]Fisher's Exact Test			
[&]Wilcoxon rank-sum test			
[#]&*P* < 0.05 indicated statistically significant differences			

6. Correlation Analysis of Baseline Concentrations of Cytokines in Aqueous Humor of DME Patients

As shown in Table 2.8 and Fig. 2.4, the VEGF factor is positively correlated with ICAM-1 ($r = 0.41$, $P = 0.010$), MCP-1 ($r = 0.40$, $P = 0.012$), IL-6 ($r = 0.33$, $P = 0.038$), and IL-8 ($r = 0.44$, $P = 0.005$), and has no correlation with IP-10 ($P > 0.05$); ICAM-1 factor is positively correlated with VEGF ($r = 0.41$, $P = 0.010$), MCP-1 ($r = 0.74$, $P < 0.001$), IP-10 ($r = 0.81$, $P < 0.001$), IL-6 ($r = 0.84$, $P < 0.001$), and IL-8 ($r = 0.55$, $P < 0.001$); MCP-1 factor is positively correlated with VEGF ($r = 0.40$, $P = 0.012$), ICAM-1 ($r = 0.74$, $P < 0.001$), IP-10 ($r = 0.70$, $P < 0.001$), IL-6 ($r = 0.74$, $P < 0.001$), and IL-8 ($r = 0.64$, $P < 0.001$); IP-10 factor is positively correlated with ICAM-1 ($r = 0.81$, $P < 0.001$), MCP-1 ($r = 0.70$, $P < 0.001$), IL-6 ($r = 0.68$, $P < 0.001$), and IL-8 ($r = 0.59$, $P < 0.001$), and has no correlation with VEGF ($P > 0.05$); IL-6 factor is positively correlated with VEGF ($r = 0.33$, $P = 0.038$), ICAM-1 ($r = 0.84$, $P < 0.001$), MCP-1 ($r = 0.74$, $P < 0.001$), IP-10 ($r = 0.68$, $P < 0.001$), and IL-8 ($r = 0.58$, $P < 0.001$); IL-8 factor is positively correlated with

VEGF (r = 0.44, P = 0.005), ICAM-1 (r = 0.55, P < 0.001), MCP-1 (r = 0.64, P < 0.001), IP-10 (r = 0.59, P < 0.001), and IL-6 (r = 0.58, P < 0.001).

Table 2.8
Correlation Analysis of Baseline Concentrations of Cytokines in Aqueous Humor of DME Patients

	ICAM-1		**MCP-1**		**IP-10**		**IL-6**		**IL-8**	
	r	***P***	***r***	***P***	***r***	***P***	***r***	***P***	***r***	***P***
VEGF	0.41	**0.010***	0.40	**0.012***	0.30	0.061	0.33	**0.038***	0.44	**0.005***
ICAM-1			0.74	**<0.001***	0.81	**<0.001***	0.84	**<0.001***	0.55	**<0.001***
MCP-1					0.70	**<0.001***	0.74	**<0.001***	0.64	**<0.001***
IP-10							0.68	**<0.001***	0.59	**<0.001***
IL-6									0.58	**<0.001***
Note: *r*: correlation coefficient										
*Spearman rank correlation test										
**P* < 0.05 indicated statistically significant differences										

7. Correlation Analysis Between Baseline Concentrations of Aqueous Humor Cytokines and OCT Biomarkers in Patients with DME

As shown in Table 2.9 and Fig. 2.5, the VEGF factor has no correlation with HRF, IRC, DRIL, discontinuity of ELM and/or EZ, SRF, and VMIA (P > 0.05); the ICAM-1 factor is positively correlated with discontinuity of ELM and/or EZ (r = 0.35, P = 0.027) and SRF (r = 0.40, P = 0.011), and has no correlation with HRF, IRC, DRIL, and VMIA (P > 0.05); the MCP-1 factor is positively correlated with HRF (r = 0.04, P = 0.020), discontinuity of ELM and/or EZ (r = 0.42, P = 0.008), and SRF (r = 0.51, P = 0.001), and has no correlation with IRC, DRIL, and VMIA (P > 0.05); the IP-10 factor is positively correlated with HRF (r = 0.34, P = 0.037), and has no correlation with IRC, DRIL, discontinuity of ELM and/or EZ, SRF, and VMIA (P > 0.05); the IL-6 factor is positively correlated with SRF (r = 0.45, P = 0.004), and has no correlation with HRF, IRC, DRIL, discontinuity of ELM and/or EZ, and VMIA (P > 0.05); the IL-8 factor is positively correlated with discontinuity of ELM and/or EZ (r = 0.37, P = 0.022), and has no correlation with HRF, IRC, DRIL, SRF, and VMIA (P > 0.05).

Table 2.9
Correlation Analysis Between Baseline Concentrations of Aqueous Humor Cytokines and OCT Biomarkers in Patients with DME

	VEGF		ICAM-1		MCP-1		IP-10		IL-6		IL-8	
	r	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*R*	*P*	*r*	*P*
HRF	-0.23	0.166	0.18	0.278	0.04	**0.020***	0.34	**0.037***	0.27	0.100	0.19	0.247
IRC	-0.06	0.708	-0.06	0.708	-0.06	0.708	-0.25	0.128	0.16	0.346	0.05	0.755
DRIL	-0.06	0.705	-0.01	0.950	0.15	0.358	0.06	0.729	0.13	0.428	0.23	0.155
ELM and/or EZ Discontinuity	0.18	0.281	0.35	**0.027***	0.42	**0.008***	0.29	0.070	0.24	0.141	0.37	**0.022***
SRF	0.21	0.202	0.40	**0.011***	0.51	**0.001***	0.30	0.062	0.45	**0.004***	0.14	0.402
VMIA	-0.15	0.357	-0.10	0.527	0.01	0.950	0.05	0.776	-0.14	0.410	0.18	0.280
Note: *r*: correlation coefficient												
*Spearman rank correlation test												
**P* < 0.05 indicated statistically significant differences												

8. Correlation Analysis between Baseline CMT and Baseline Concentrations of Aqueous Humor Cytokines in DME Patients

As shown in Table 2.10, baseline CMT is positively correlated with VEGF ($r = 0.33$, $P = 0.040$), and not correlated with ICAM-1, MCP-1, IP-10, IL-6, and IL-8 ($P>0.05$).

Table 2.10
Correlation Analysis between Baseline CMT and Baseline Concentrations of Aqueous Humor Cytokines in DME Patients

	VEGF		ICAM-1		MCP-1		IP-10		IL-6		IL-8	
	r	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*R*	*P*	*r*	*P*
CMT	0.33	**0.040***	0.12	0.487	0.06	0.729	-0.08	0.619	0.11	0.501	-0.12	0.472
Note: *r*: correlation coefficient												
*Spearman rank correlation test												
**P* < 0.05 indicated statistically significant differences												

9. ROC Curves of Various Biomarkers Predicting the Prognosis of Anti-VEGF Treatment in DME

According to the aforementioned difference analyses, there were statistically significant differences ($P<0.05$) between the good response group and poor response group in aqueous humor cytokines VEGF, IP-10, and IL-8, peripheral blood inflammatory indicators SII and SIRI, lipid index TC, renal function index Cys-C, baseline CMT, and OCT biomarkers HRF, DRIL, and VMIA. The predictive ability of various biomarkers for the prognosis of anti-VEGF treatment in DME was determined by plotting ROC curves.

As shown in Table 2.12 and Fig. 2.6, the area under the ROC curve (AUC) for VEGF predicting the prognosis of anti-VEGF treatment is 0.69, with a 95% confidence interval (95% CI) of 0.704–0.930, $P = 0.043$; for IP-10, the AUC was 0.70, 95% CI 0.54–0.86, $P = 0.033$; for IL-8, the AUC was 0.72, 95% CI 0.55–0.90, $P = 0.023$; for SII, the AUC was 0.72, 95% CI 0.56–0.89, $P = 0.020$; for SIRI, the AUC was 0.71, 95% CI 0.54–0.88, $P = 0.022$; for TC, the AUC was 0.74, 95% CI 0.57–0.90, $P = 0.011$; for Cys-

C, the AUC was 0.75, 95% CI 0.59–0.90, *P* = 0.009; for baseline CMT, the AUC was 0.80, 95% CI 0.65–0.95, *P* = 0.002; for HRF, the AUC was 0.77, 95% CI 0.61–0.92, *P* = 0.004; for DRIL, the AUC was 0.71, 95% CI 0.54–0.88, *P* = 0.024; for VMIA, the AUC was 0.70, 95% CI 0.53–0.87, *P* = 0.034.

Table 2.12
Areas Under the ROC Curves of Various Biomarkers

VEGF	**AUC**	**95% CI**	***P* Value**
	0.69	**0.51–0.87**	**0.043**
IP-10	0.70	0.54–0.86	0.033
IL-8	0.72	0.55–0.90	0.023
SII	0.72	0.56–0.89	0.020
SIRI	0.71	0.54–0.88	0.022
TC	0.74	0.57–0.90	0.011
Cys-C	0.75	0.59–0.90	0.009
Baseline CMT	0.80	0.65–0.95	0.002
HRF	0.77	0.61–0.92	0.004
DRIL	0.71	0.54–0.88	0.024
VMIA	0.70	0.53–0.87	0.034
Note: *P* < 0.05 indicated statistically significant differences			

4. Discussion

DME is one of the primary microvascular complications of diabetes and a significant cause of vision impairment in patients. Epidemiological data indicate a global incidence of DME of 5.47%[4], with a pathogenesis that remains highly complex and not fully elucidated. The key pathogenic mechanisms involve disruption of the blood-retinal barrier (BRB), dysfunction in fluid drainage by Müller glial cells and retinal pigment epithelium (RPE) cells[5, 6], and prominent inflammatory responses[7]. Although intravitreal anti-VEGF therapy remains the first-line treatment, patient responses exhibit substantial heterogeneity: over 30% of patients demonstrate persistent macular edema after six consecutive injections[8]. This variability suggests the involvement of multifactorial interactive mechanisms.

This study developed a comprehensive predictive model for anti-VEGF treatment response in DME patients by integrating multidimensional biomarkers, including aqueous humor inflammatory factors, peripheral blood biochemical parameters, and OCT imaging features. In contrast to conventional approaches focusing on isolated factors, the present investigation revealed synergistic interactions among the inflammatory microenvironment (e.g., elevated IL-6 and MCP-1 levels in aqueous humor), dyslipidemia (high TC), and retinal structural abnormalities (such as subretinal fluid and ellipsoid zone disruption). These factors collectively contribute to differential treatment responses by exacerbating BRB breakdown and impairing Müller cell-mediated fluid clearance. The findings provide a multimodal data-driven theoretical foundation for precision medicine in DME, addressing limitations of earlier single-factor predictive models. Subsequent sections will stratify and discuss the principal outcomes of this study to identify critical biomarkers influencing anti-VEGF responsiveness and explore their underlying mechanisms.

4.1 Effects of General Data on the Prognosis of Anti-VEGF Treatment in DME Patients

This study systematically collected general demographic and clinical parameters from DME patients to investigate their association with responses to anti-VEGF therapy. Consistent with previous reports [9, 10], no significant differences were observed in baseline characteristics such as age, gender, or laterality between the responsive and non-responsive groups, further confirming that these factors do not substantially influence treatment outcomes. Regarding glycemic control metrics, FPG levels showed no statistical difference between groups, which may be attributed to overall standardized glucose-lowering management and generally well-controlled blood glucose levels among the enrolled patients. Concerning long-term glycemic control as reflected by HbA1c, although multiple studies have proposed HbA1c as a potential predictor of anti-VEGF treatment response [11–14], this study did not identify a significant intergroup difference in HbA1c levels. This finding aligns with recent investigations[15, 16], suggesting that HbA1c may not possess independent prognostic value for DME treatment outcomes, as its role is likely modulated by multiple factors including baseline patient characteristics, therapeutic context, and overall metabolic status.

Notably, the majority of patients in this cohort had received systematic endocrine interventions and maintained relatively stable glycemic control (HbA1c ranging between 7% and 8%), which may explain the lack of significant HbA1c difference between groups. This phenomenon implies that once glycemic control reaches a certain threshold, its impact on the retinal microenvironment and anti-VEGF responsiveness may plateau, while other local or systemic factors—such as inflammatory status, lipid metabolism, and retinal structural changes—may play more critical regulatory roles. Therefore, greater emphasis should be placed on multidimensional biomarker integration for predicting treatment outcomes, which represents the core focus of this investigation.

This study has inherent limitations, including a relatively small sample size and single-center design, which may affect the generalizability of the findings. Additionally, potential confounding factors such as glycemic variability, duration of diabetes, and other comorbidities were not fully adjusted for. Future large-scale, multicenter prospective studies are warranted to validate the relationship between HbA1c and anti-VEGF treatment response, and to elucidate the mechanistic basis of heterogeneous therapeutic outcomes in DME through integrated multi-omics approaches.

- 4.2 Effects of Baseline Aqueous Humor Cytokines on the Prognosis of Anti-VEGF Treatment in DME Patients

This study focused on the impact of baseline aqueous humor cytokine levels on the prognosis of anti-VEGF therapy in patients with DME. Previous studies have consistently demonstrated abnormal expression of multiple cytokines in the aqueous humor of DME patients, which collectively contribute to disease pathogenesis and progression [17–19]. Kim et al.[20] further elucidated the critical role of inflammation- and angiogenesis-related cytokines in the pathological mechanisms of DME. The present study also confirmed that the concentrations of VEGF, ICAM-1, IL-6, and IL-8 in the aqueous humor were significantly elevated in DME patients compared to normal controls, corroborating existing literature and underscoring the core feature of DME as a multifactor-mediated inflammatory and vascular disease.

VEGF, as a central pathogenic factor in DME, is upregulated in the hypoxic retinal microenvironment induced by hyperglycemia. By binding to VEGFR, it enhances vascular permeability, promotes leakage and neovascularization, ultimately leading to macular edema [24]. Although some studies have suggested that DME patients with higher baseline aqueous VEGF levels exhibit poorer responses to anti-VEGF therapy [21, 22], this study revealed that patients with a favorable response to anti-VEGF therapy actually had higher baseline VEGF levels (responsive group: 22.7 pg/ml vs. non-responsive group: 6.72 pg/ml). This suggests that high VEGF expression may represent a DME subtype primarily characterized by vascular leakage, which responds better to VEGF blockade strategies. Conversely, in patients with lower VEGF levels, inflammatory mechanisms may predominate, potentially explaining the suboptimal response to anti-VEGF therapy and the better clinical response to corticosteroid treatment observed in this subgroup.

Interferon-inducible protein 10 (IP-10), a non-angiogenic chemokine primarily induced by interferon-gamma, recruits T cells, monocytes, and NK cells to the retina, amplifies immune-inflammatory responses, and contributes to blood-retinal barrier disruption [23]. Consistent with previous findings [24, 25], this study observed significantly elevated IP-10 levels in the non-responsive group (P = 0.033), and it showed significant positive correlations with inflammatory factors such as MCP-1, IL-6, and IL-8 ($r \geq 0.68$, $P < 0.001$). This further supports the role of IP-10 as a key coordinator within the inflammatory network, potentially diminishing the efficacy of anti-VEGF therapy by amplifying inflammatory responses.

IL-8 is a pro-inflammatory and pro-angiogenic cytokine whose canonical biological effects include the chemotaxis and activation of neutrophils. It contributes to neutrophil-mediated tissue damage and exacerbates vascular leakage and disruption of intercellular junctions via the CXCR1/CXCR2 signaling pathway, participating in DME pathogenesis independently of the VEGF pathway [26, 27]. This may explain why anti-VEGF therapy alone often fails to control IL-8-driven DME progression [28]. Aligning with the results of the prospective study by Kwon et al.[29], the present study also demonstrated significantly higher expression of IL-8 in the non-responsive group (P = 0.025), with a moderate correlation observed with VEGF ($r = 0.44$, $P = 0.005$). This indicates that IL-8 may act synergistically with VEGF or serve as an alternative pathway leading to treatment resistance. Furthermore, studies have found that intravitreal triamcinolone acetonide is effective in patients unresponsive to anti-VEGF therapy, and this therapeutic effect correlates with aqueous IL-8 levels[30], suggesting that elevated IL-8 may be a useful biomarker for identifying a DME patient subgroup suitable for early anti-inflammatory intervention.

In summary, this study indicates that baseline aqueous levels of VEGF, IP-10, and IL-8 can serve as biomarkers for predicting the response to anti-VEGF therapy in DME patients. It not only reinforces the central role of VEGF in DME but also highlights the significant contribution of inflammatory factors like IP-10 and IL-8 in mediating treatment resistance. The pathogenesis of DME is far more complex than can be explained by the VEGF pathway alone, involving an intricate network where angiogenesis and immune inflammation intersect. This study provides a theoretical basis for the precise subtyping of DME and the selection of treatment strategies. Future research should further explore the interactions among these factors and the clinical value of combined interventions targeting multiple mechanisms.

- 4.3 Effects of Peripheral Blood Inflammatory Indicators on the Prognosis of Anti-VEGF Treatment in DME Patients

DME, as a retinal disease closely associated with chronic low-grade systemic inflammation, involves not only the local ocular microenvironment but also systemic immune-inflammatory status. In recent years, peripheral blood inflammatory indices have emerged as valuable tools for assessing systemic inflammation in DME patients, offering new perspectives for understanding its pathological mechanisms and heterogeneous treatment responses. This study compared peripheral blood inflammatory indices between DME patients and normal controls, revealing significantly elevated levels of neutrophil count (Neut), neutrophil-to-lymphocyte ratio (NLR), systemic immune-inflammation index (SII), systemic inflammation response index (SIRI), derived neutrophil-to-lymphocyte ratio (dNLR), and monocyte-to-granulocyte ratio (M/GLR) in DME patients. These findings further support the critical role of systemic inflammation in the pathogenesis of DME.

When evaluating differential responses to anti-VEGF therapy, this study demonstrated that the poor-response group exhibited significantly higher SII and SIRI levels compared to the good-response group, with statistically significant differences. This suggests that these composite inflammatory indices may serve as predictive biomarkers. SII integrates neutrophil, lymphocyte, and platelet counts, providing a comprehensive reflection of the balance between inflammatory and immune status. Due to its calculation method being less influenced by individual physiological fluctuations, SII offers a more stable representation of overall systemic inflammation. Previous studies have shown a positive correlation between SII and the presence and severity of diabetic retinopathy (DR) and DME [31–33]. For instance, Özata et al. reported significantly elevated SII in DME patients with cystoid macular edema[34]. In contrast, SIRI, initially valuable in prognostic assessment in oncology and calculated based on neutrophil, monocyte, and lymphocyte counts, has recently been recognized for its predictive significance in chronic metabolic inflammatory diseases such as type 2 diabetes. It may serve as a valuable biomarker for early screening of DR [35]. Emerging mechanistic studies indicate that elevated SIRI may reflect sustained activation of bone

marrow-derived immune cells, increased release of inflammatory mediators, and the formation of an immunosuppressive microenvironment. Furthermore, SIRI is closely associated with vascular endothelial dysfunction and microcirculatory impairment, which may represent potential mechanisms underlying its relationship with DME development and anti-VEGF treatment response.

The results of this study indicate that SII and SIRI not only serve as reliable indicators of systemic inflammation in DME patients but also hold potential for predicting individual responses to anti-VEGF therapy. Elevated SII/SIRI levels may identify a subgroup of DME patients characterized by excessive inflammatory responses and poor anti-VEGF treatment outcomes. This provides a theoretical basis for early identification of treatment-resistant DME patients in clinical practice and for developing individualized treatment strategies, such as combination anti-inflammatory therapy. However, current research on the prognostic value of SII and SIRI in anti-VEGF therapy for DME remains limited. Future large-scale, multicenter studies are warranted to further validate their clinical utility.

- 4.4 Effects of Indicators Such as Blood Lipids and Renal Function on the Prognosis of Anti-VEGF Treatment in DME Patients

The pathogenesis of diabetic macular edema (DME) involves multisystem interactions, extending beyond local VEGF signaling pathway activation to include critical roles of systemic metabolic and inflammatory status. This study demonstrated significantly elevated levels of total cholesterol (TC) and cystatin C (Cys-C) in the poor-response group compared to the good-response group following anti-VEGF therapy, with other lipid and renal function parameters also showing upward trends. These observations suggest that dyslipidemia and renal impairment collectively contribute to clinical treatment resistance in DME. Notably, ROC analysis further confirmed the strong predictive value of baseline Cys-C for treatment prognosis (AUC = 0.75, P = 0.009). This finding not only aligns with previous reports indicating that refractory DME is often associated with more significant systemic comorbidities[36], but also highlights the potential of lipid and renal parameters as biomarkers for precision medicine in DME.

Blood lipids, comprising various lipid components in plasma, are essential for fundamental cellular metabolism. Dyslipid exacerbates DME pathogenesis through multiple mechanisms. Abnormal accumulation of lipid components such as TC promotes the formation of advanced glycation end products (AGEs), activates oxidative stress and release of inflammatory mediators, thereby compromising blood-retinal barrier integrity. Subsequent leakage of lipids and lipoproteins into the interstitial space creates a microenvironment conducive to DME development and persistence [37, 38]. Elevated TC levels have been consistently associated with increased DME risk and diminished anti-VEGF treatment response in multiple studies [39–41]. Warid et al.[42] reported that high TC levels correlate with poorer anatomical outcomes after anti-VEGF therapy, consistent with the clinical observations in this study. This suggests that in some DME patients, a lipotoxic microenvironment may attenuate the efficacy of anti-VEGF agents, indicating that disease progression is not solely driven by VEGF pathway activation. Therefore, intensive lipid-lowering therapy may represent a crucial strategy for optimizing treatment outcomes in dyslipidemic patients by reducing lipid peroxidation and inflammatory responses.

Diabetic nephropathy has been frequently associated with the development and progression of DME. Hwang et al.[43] observed that macular edema alleviated following initial dialysis in chronic kidney disease patients, suggesting that renal function may influence both the occurrence and treatment response of DME. Additional studies have demonstrated that patients with elevated serum creatinine and reduced glomerular filtration rate exhibit poorer responses to anti-VEGF injections[44, 45]. Notably, the relationship between renal impairment and DME extends beyond traditional parameters such as glomerular filtration rate, with Cys-C emerging as a sensitive marker revealing deeper connections with microvascular complications. Elevated Cys-C levels not only reflect reduced glomerular filtration function but have also been shown to participate directly or indirectly in diabetic microangiopathy[46–48]. For instance, Cys-C can promote vascular leakage by upregulating VEGF expression[49] and form positive feedback loops with proinflammatory cytokines such as IL-6 and IL-8[50]. This study identified significantly higher Cys-C levels in the poor-response group, potentially attributable to more intense inflammatory reactions leading to inferior outcomes after anti-VEGF therapy. Our data also revealed positive correlations

between Cys-C and inflammatory indices such as NLR[51], suggesting its potential role as a hub molecule connecting metabolic disorders, low-grade inflammation, and treatment resistance in DME. Although the precise mechanisms of Cys-C in DME remain incompletely elucidated, its high predictive accuracy (AUC = 0.75) offers a practical tool for early identification of refractory cases and underscores the necessity of renal function management in comprehensive DME treatment.

In conclusion, this study substantiates the significance of lipid and renal parameters (particularly TC and Cys-C) in DME treatment resistance from both clinical and molecular perspectives. These findings not only provide a theoretical foundation for personalized DME treatment but also emphasize the future importance of therapeutic strategies targeting multisystem coordination.

- 4.5 Effects of Baseline CMT and OCT Biomarkers on the Prognosis of Anti-VEGF Treatment in DME Patients
- Optical coherence tomography (OCT), as a cornerstone tool for the diagnosis and management of diabetic macular edema (DME), provides not only high-resolution retinal structural imaging but also enables dynamic monitoring of disease progression and treatment response through quantitative parameters such as central macular thickness (CMT). This study identified significantly lower baseline CMT in the poor-response group compared to the good-response group (P = 0.001), consistent with previous reports suggesting that thinner CMT may predict suboptimal edema resolution[52]. This phenomenon may reflect irreversible retinal structural damage due to chronic edema or indicate the presence of fibrosis-dominated non-edematous pathological changes in the low-CMT subgroup, thereby diminishing the efficacy of anti-VEGF therapy. Furthermore, OCT-derived biomarkers including HRF, DRIL, and VMIA were significantly more prevalent in the poor-response group (P < 0.05), underscoring the multidimensional value of OCT in predicting treatment resistance.
- HRF in DME are considered precursors of hard exudates, closely associated with lipoprotein extravasation following blood-retinal barrier disruption and accumulation of lipid-laden macrophages[53–55]. Some researchers have proposed that HRF may represent activated and migrating retinal microglia, serving as inflammatory biomarkers in various retinal diseases[56]. The findings of this study further support the inflammatory relevance of HRF. We observed that the presence of HRF correlated with specific aqueous humor inflammatory factors, notably showing a positive correlation with IP-10 (r = 0.34, P = 0.037), suggesting that HRF may serve as morphological markers of the retinal inflammatory microenvironment. More importantly, baseline HRF count demonstrated significant association with anti-VEGF treatment outcomes: the poor-response group showed significantly higher HRF prevalence (P < 0.001), and baseline HRF exhibited considerable predictive power for treatment prognosis (AUC = 0.77, P = 0.004). These findings not only validate HRF as indicators of unfavorable DME prognosis but also emphasize their clinical utility in identifying anti-VEGF treatment resistance. The strong association between HRF and inflammation is further elucidated by differential treatment responses. For instance, in refractory DME, dexamethasone implants have demonstrated superior efficacy in reducing HRF number compared to anti-VEGF agents[57], consistent with the positive correlation between HRF and inflammatory factors observed in this study. This suggests that HRF accumulation may stem from VEGF-independent inflammatory pathway activation. Consequently, the presence of HRF not only predicts poor anti-VEGF response but may also indicate patients who would benefit more from anti-inflammatory strategies, thereby enhancing our understanding of DME heterogeneity and providing a rationale for personalized treatment.
- DRIL represents another critical OCT parameter, reflecting damage to ganglion cell axons, bipolar cells, and amacrine cells, resulting in disruption of visual signal transmission pathways[58]. Its pathogenesis likely involves multifactorial interactions: chronic macular edema may cause mechanical stretching beyond the elastic limits of retinal neuronal structures [59, 60], while macular ischemia-induced capillary nonperfusion can exacerbate DRIL progression[61], indicating that DRIL constitutes structural damage resulting from combined edema and ischemic effects. DRIL may gradually resolve over time or with treatment, during which the signaling pathway from photoreceptors to ganglion cells is restored, accompanied by visual function improvement. Thus, DRIL serves as a biomarker for early treatment prognosis. This study further confirmed the clinical value of DRIL: baseline DRIL presence significantly correlated with poor anti-VEGF treatment response (higher prevalence in poor-response group, P = 0.003), and demonstrated predictive value for treatment outcomes (AUC = 0.71, P = 0.024). These findings suggest that DRIL not only represents irreversible microstructural damage but may also serve as a sensitive indicator of early treatment response. Notably, DRIL

improvement appears treatment-dependent: dexamethasone implants can promote DRIL resolution through potent anti-inflammatory effects[62]. This contrasts with the lack of direct correlation between DRIL and inflammatory factors observed in our study, indicating that while DRIL progression may be mechanically driven, its resolution benefits from anti-inflammatory intervention. Therefore, DRIL presence not only identifies treatment resistance risk but also highlights the necessity for combination therapies targeting structural damage (such as anti-VEGF and corticosteroid sequential therapy), providing a theoretical basis for optimized treatment strategies.

- VMI constitutes an important factor influencing treatment outcomes in retinal vascular and macular diseases[63]. OCT analysis in this study revealed significantly poorer anti-VEGF treatment response in patients with VMIA (P = 0.005), consistent with previous reports associating VMIA with unfavorable visual prognosis and limited anatomical improvement [64, 65], which is similar to our study findings. Gong et al. further demonstrated that VMIA correlates with reduced CMT decrease at 1 month and limited visual improvement during 12-month follow-up[66]. The mechanisms underlying VMIA's effect on treatment response may involve multiple pathways: mechanically, vitreomacular traction or epiretinal membrane formation generates multidimensional stress leading to retinal displacement and foveal microstructural disruption[67] ; molecularly, VMIA promotes accumulation of inflammatory factors including VEGF, fibroblast growth factor, and IL-6 in the macular region, inducing chronic inflammation and altered vascular permeability[68–70]. Particularly noteworthy is our finding of positive correlations between VMIA and multiple aqueous humor inflammatory factors, providing new insights into its molecular mechanisms. These findings carry important clinical implications: first, VMIA may serve as a significant biomarker for predicting anti-VEGF treatment response; second, combined vitrectomy to relieve mechanical traction with anti-VEGF therapy may yield better outcomes in patients with VMIA. This study not only deepens our understanding of DME pathophysiology but also provides a theoretical foundation for personalized treatment strategies. Future research should further explore the association between VMIA and specific molecular pathways, as well as optimal timing and protocols for combination therapies.

5. Conclusion

This study integrated the local ocular microenvironment, systemic inflammatory-metabolic status, and multimodal imaging features to systematically elucidate a predictive model for anti-vascular endothelial growth factor (anti-VEGF) treatment response in diabetic macular edema (DME). The findings revealed that the aqueous humor inflammatory factor profile (VEGF, IP-10, IL-8), peripheral blood inflammatory composite indices (SII, SIRI), lipid metabolism parameters (TC), renal function markers (Cys-C), and optical coherence tomography (OCT) structural biomarkers (CMT, HRF, DRIL, VMIA) collectively constitute a predictive framework for DME treatment outcomes. Particularly noteworthy, lower baseline VEGF levels accompanied by elevated IP-10 and IL-8 suggest that inflammatory microenvironments may precede VEGF pathway activation; increased TC and Cys-C reflect synergistic exacerbation of vascular leakage and treatment resistance through dyslipidemia and renal impairment; while reduced CMT and the presence of HRF, DRIL, and VMIA further demonstrate interactions between structural damage and chronic inflammation. These indicators represent critical factors contributing to suboptimal anti-VEGF therapy responses in DME patients.

These discoveries not only deepen the understanding of DME treatment resistance mechanisms—specifically, how VEGF-independent inflammatory activation, metabolic dysfunction, and retinal structural remodeling collectively drive therapeutic failure—but also offer quantifiable decision-support tools for clinical practice. Based on these multidimensional biomarkers, a prognostic stratification system for DME could be developed to guide personalized treatment strategies: for example, patients with high inflammatory burdens might benefit from prioritized corticosteroid therapy; those with metabolic abnormalities may require combined systemic interventions; and individuals with significant structural damage could necessitate early combination with vitreoretinal interface surgery. This study advances precision medicine in DME from molecular to imaging dimensions and provides a theoretical foundation for combination therapies targeting multiple mechanisms.

Declarations

Disclosures:

None of the authors have any commercial or financial relationships that could inappropriately influence this work. All authors declare no conflicts of interest.

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Author Contribution

R.T.S. (co-first author): designed the study, analyzed the data, and drafted the main manuscript text.S.X.Y. (co-first author): collected clinical and experimental data, sampled specimens, and revised the initial manuscript draft.H.Q. and B.L.: performed experimental measurements and verified data accuracy.J.J.S.: contributed to data interpretation and statistical analysis optimization.L.Z. (corresponding author): conceived and supervised the entire study, critically revised the manuscript for important intellectual content, and secured research funding.All authors reviewed and approved the final version of the manuscript.

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Data Availability

The datasets generated and/or analyzed during the current study are not publicly available due to patient privacy and ethical restrictions, but are available from the corresponding author on reasonable request.

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Figures

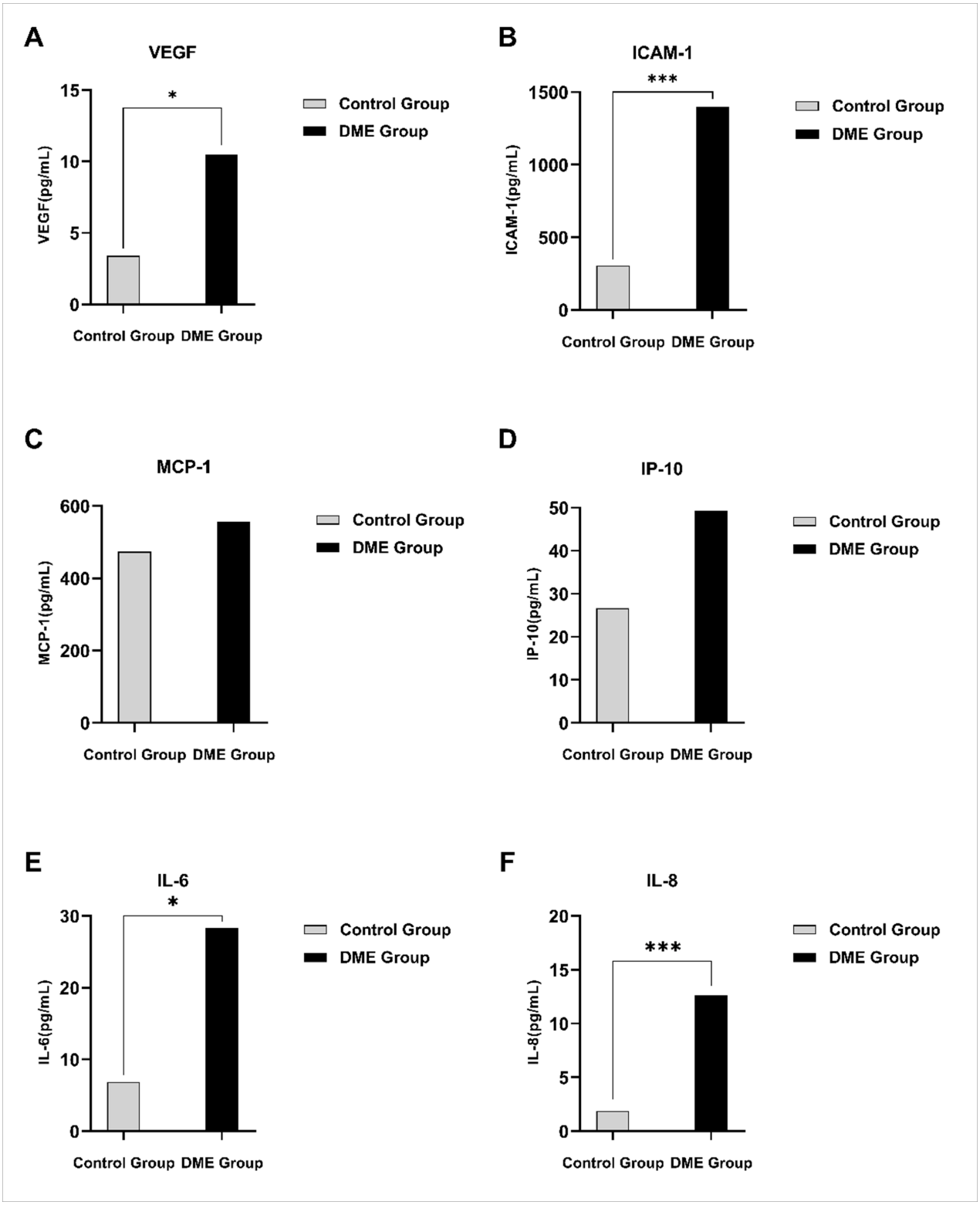


Figure 1

Comparison of Baseline Concentrations of Aqueous Humor Cytokines Between Control Group and DME Group

Note: *P□0.05 indicated statistically significant differences; ***P□0.001 indicated statistically significant difference

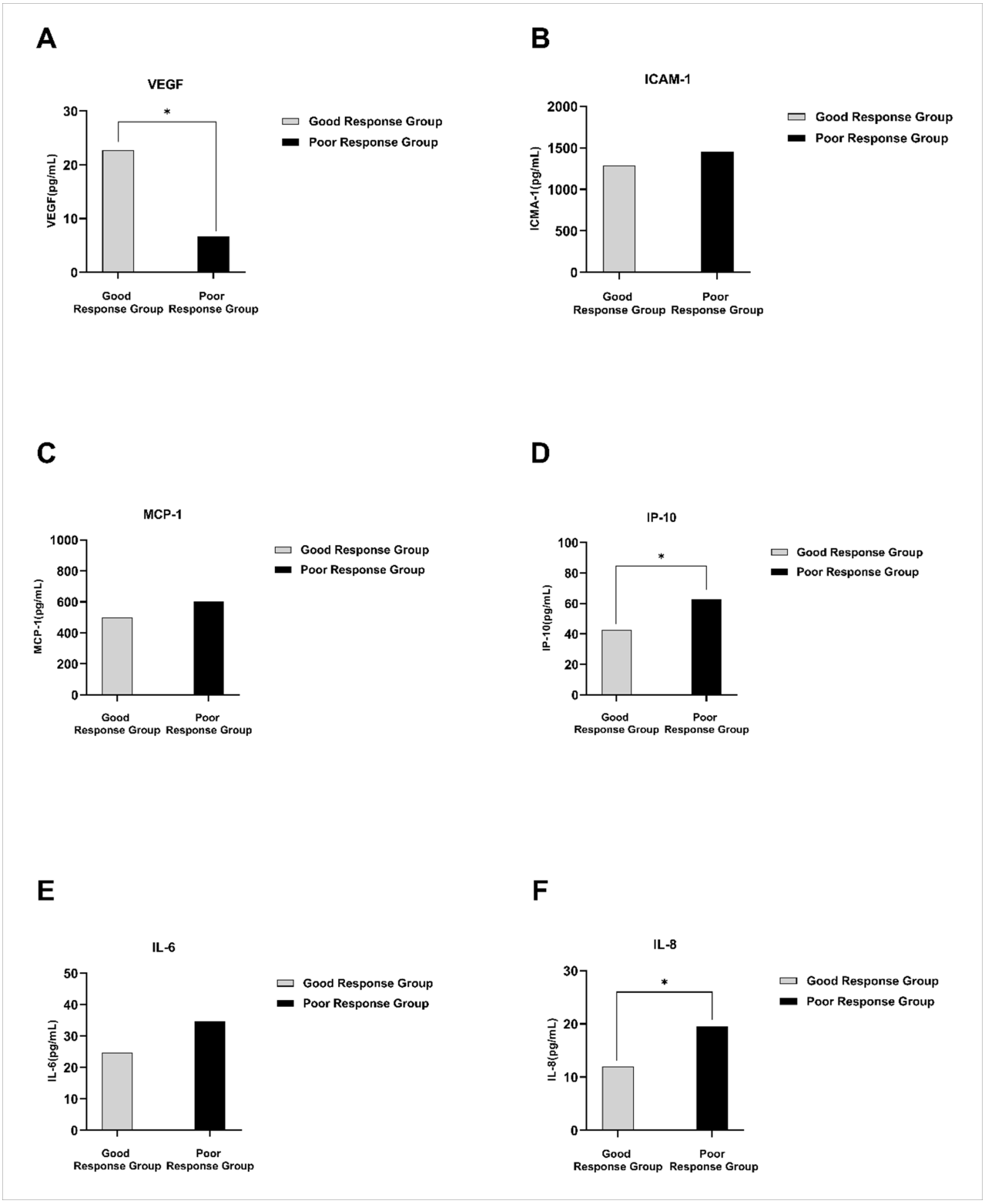


Figure 2

Comparison of Baseline Concentrations of Cytokines in Aqueous Humor Between Good Response Group and Poor Response Group

Note: *P<0.05 indicated statistically significant differences

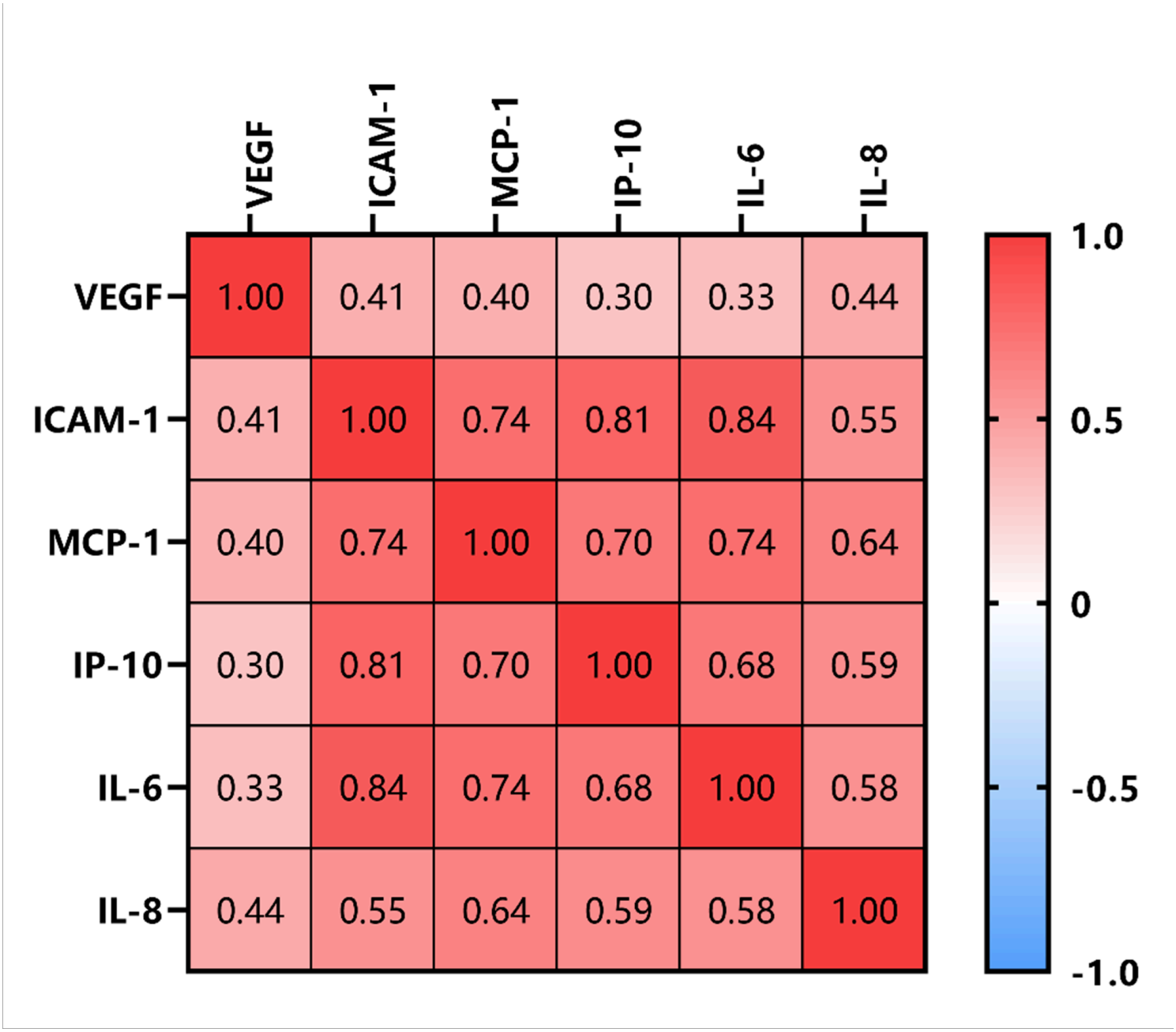


Figure 3

Figure 2.4 Heat Map of Baseline Concentration Correlation Analysis of Cytokines in Aqueous Humor of DME Patients

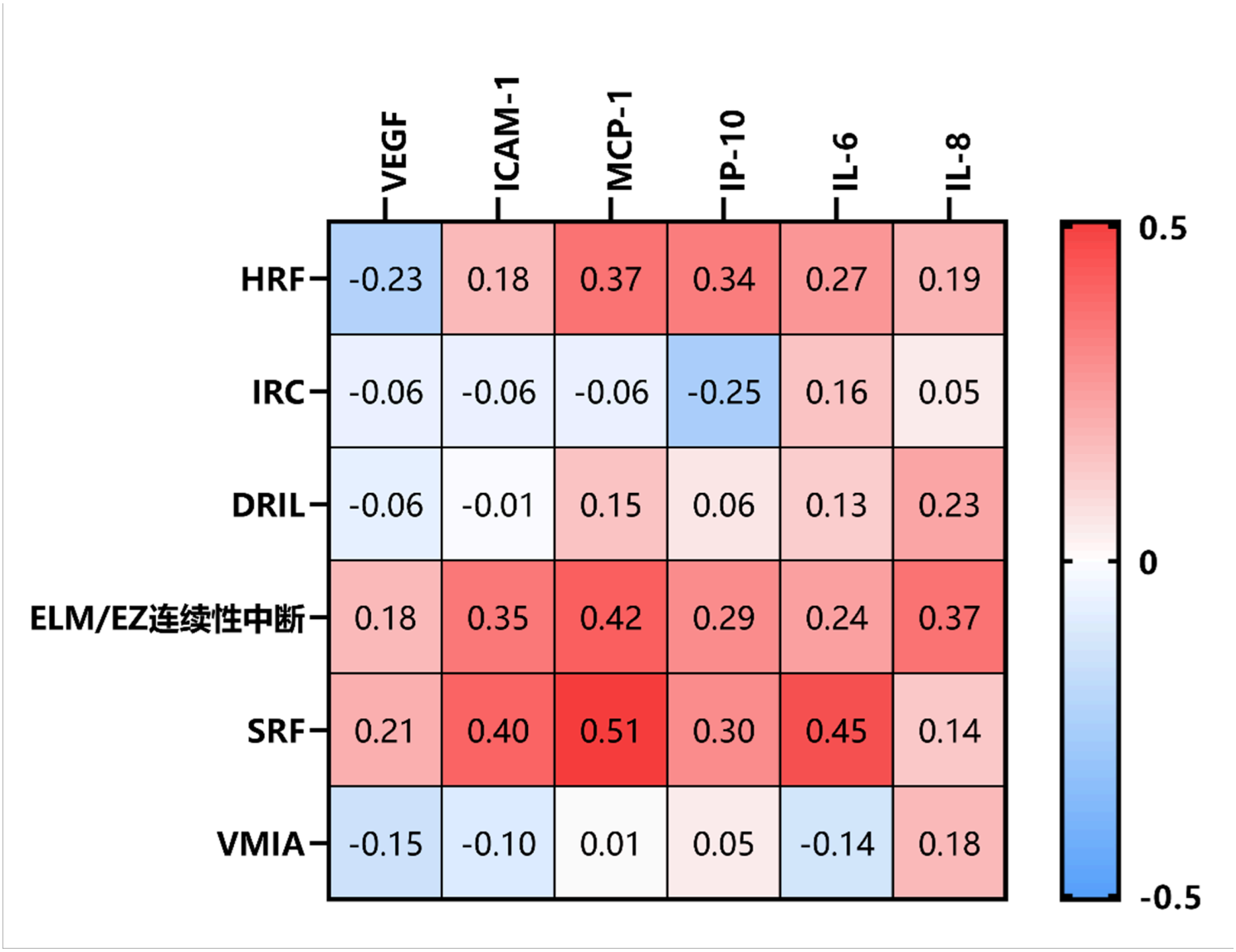


Figure 4

Figure 2.5 Heat Map of Correlation Analysis Between Baseline Concentrations of Aqueous Humor Cytokines and OCT Biomarkers in Patients with DME

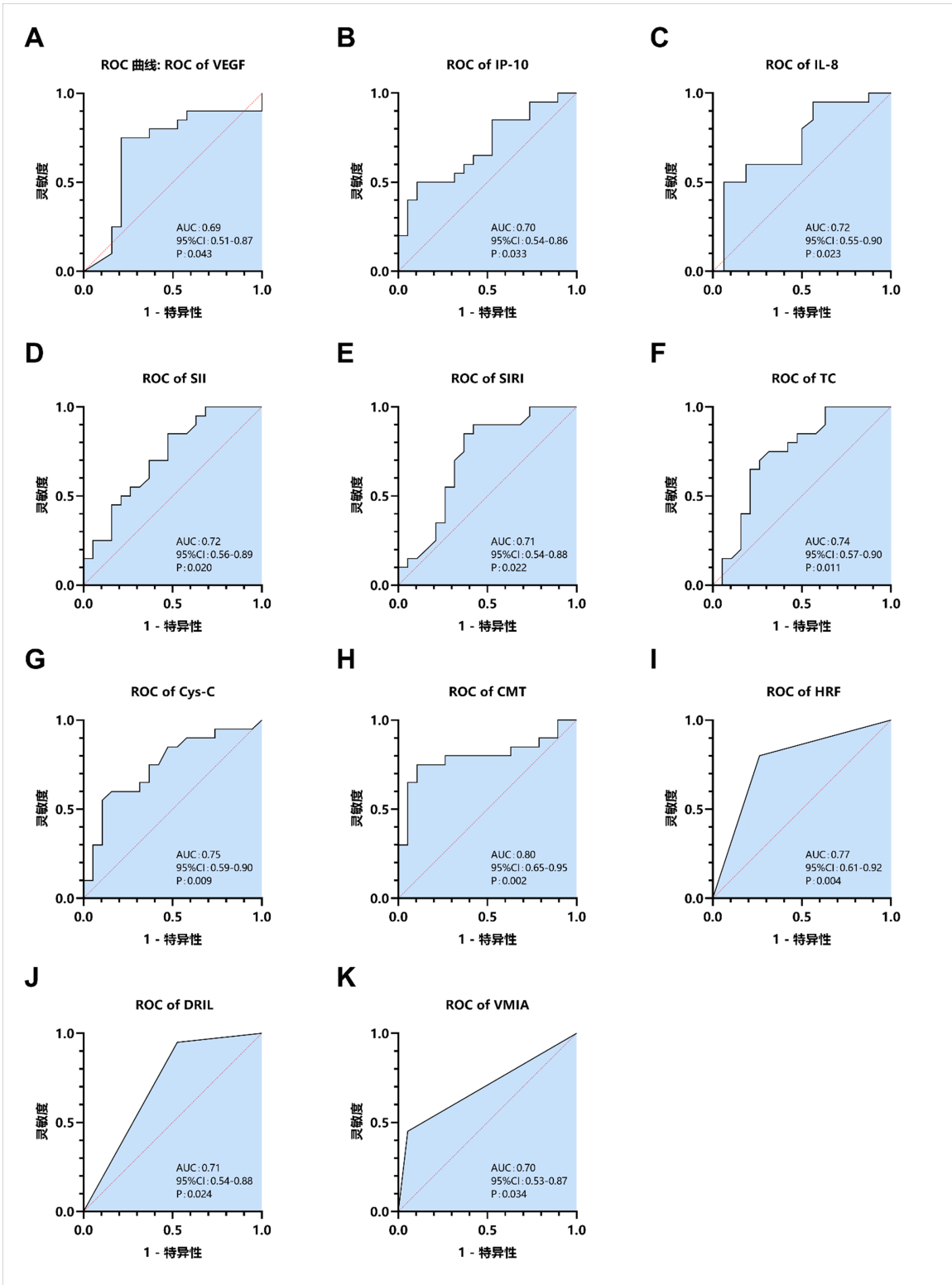


Figure 5

Figure 2.6: ROC Curves of Various Biomarkers Predicting the Efficacy of Anti-VEGF Treatment