Original Article

# Multidimensional Clinical Phenotyping and Its Predictive Interaction with Structural–Functional Severity Endpoints in Diabetic Macular Edema: A Hospital-Based Systems-Biomarker Analysis

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## Abstract

**Background:** To examine how multidimensional clinical phenotypes—spanning metabolic, vasculopathic, renal, inflammatory, and lifestyle domains—interact with structural and functional severity endpoints in diabetic macular edema (DME), using a hospital-based systems-biomarker model. **Material and Methods:** A cross-sectional analysis was conducted on patients with OCT-confirmed DME. Clinical phenotyping encompassed glyco-inflammatory load (HbA1c, CRP), metabolic–vascular indices (BP, lipid profile), renal microangiopathy (microalbuminuria, creatinine, eGFR), and lifestyle factors (BMI, smoking). Structural endpoints (central macular thickness, intraretinal cysts, DRIL, ELM/EZ integrity, choroidal thickness) and functional endpoints (best-corrected visual acuity, contrast sensitivity) were analyzed. Advanced multivariate interaction modeling and systems-biomarker scoring were performed. **Results:** A composite phenotype panel (HbA1c, microalbuminuria, LDL, systolic BP) explained 71.4% of structural severity variance. Glyco-inflammatory load highly correlated with DRIL and ELM/EZ disruption ($r = 0.622$, $p < 0.001$). Renal microangiopathy markers were independently tied to diffuse cystoid edema, and hypertension was a strong predictor of chronic edema. EZ disruption and DRIL extent were the most robust predictors of visual dysfunction. **Conclusion:** DME severity is orchestrated through synergistic, not isolated, systemic derangements. Systems-biomarker models offer powerful tools for predicting retinal injury and vision loss, underscoring the value of multidomain clinical profiling in precision management.

**Keywords:** DME, systems biomarkers, clinical phenotyping, DRIL, ELM/EZ integrity, metabolic dysregulation, retinal neurodegeneration.

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## Introduction

Diabetic macular edema (DME) represents a quintessential neurovascular complication of diabetes, marked by chronic metabolic dysfunction, microvascular instability, and retinal disorganization. Classical approaches relying on glycemia alone often fail to capture the heterogeneity in DME presentation and progression. Increasingly, evidence demonstrates the centrality of multidomain systemic influences—including metabolic, renal, vascular, lipid, and inflammatory factors—in shaping macular edema phenotypes.

**The Evolution of DME Understanding:** Traditional DME management has focused primarily on hyperglycemia as the principal driver of retinal microvascular complications. However, clinical observations consistently reveal that patients with similar glycemic control exhibit markedly different DME phenotypes, response patterns to therapy, and visual outcomes. This heterogeneity suggests that DME pathogenesis extends beyond glucose toxicity to encompass a complex interplay of systemic pathophysiologic mechanisms.

Recent advances in retinal imaging, particularly spectral-domain optical coherence tomography (SD-OCT), have enabled detailed characterization of macular structural changes. These technologies reveal that DME is not merely a fluid accumulation disorder but involves progressive neurodegeneration, manifesting as disorganization of retinal inner layers (DRIL), photoreceptor disruption (ELM/EZ integrity loss), and microvascular dropout.

**The Systems-Biomarker Paradigm:** The concept of systems biomarkers represents a paradigm shift from reductionist, single-marker approaches to integrated, multidomain profiling. In DME, this framework recognizes that retinal injury emerges from the convergence of multiple pathophysiologic axes:

- Glyco-inflammatory axis: Chronic hyperglycemia induces oxidative stress, advanced glycation end-products (AGEs), and inflammatory cytokine release, directly damaging retinal neurons and vascular endothelium.
- Metabolic-vasculopathic axis: Hypertension and dyslipidemia compromise endothelial integrity, alter blood-

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retinal barrier permeability, and promote chronic fluid extravasation.
- Renal microangiopathy axis: Albuminuria and reduced glomerular filtration reflect systemic microvascular dysfunction that parallels retinal capillary pathology.
- Lifestyle and anthropometric modifiers: Obesity and smoking introduce additional inflammatory burden and microvascular compromise.
- Retinal structural domain: Modern imaging biomarkers (DRIL, ELM/EZ disruption, choroidal thinning) serve as integrative readouts of cumulative systemic insults.

**Study Rationale and Objectives**

This study proposes and tests a hospital-based systems-biomarker framework, integrating multidimensional clinical phenotyping with advanced imaging severity endpoints, to quantify and model their predictive interaction on DME structure and function. Specific objectives include:

- To comprehensively phenotype DME patients across glyco-inflammatory, metabolic-vascular, renal, and lifestyle domains.
- To characterise structural severity using validated OCT biomarkers (CMT, DRIL, ELM/EZ integrity, cystoid morphology, choroidal thickness).
- To assess functional severity through BCVA and contrast sensitivity measurements.
- To develop multivariate interaction models quantifying the predictive relationship between clinical phenotypes and retinal severity endpoints.
- To construct a composite systems-biomarker scoring system for DME severity stratification.

## Materials and Methods

**Study Design and Setting**

This cross-sectional observational study was conducted at a tertiary ophthalmology centre in Kashmir, India, specialising in diabetes-related retinal disease management. The centre serves a diverse patient population with high diabetic retinopathy prevalence. The study protocol received institutional ethics committee approval and adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all participants.

**Study Population**

**Inclusion Criteria:**

- Age 30–80 years
- Confirmed diagnosis of type 2 diabetes mellitus (WHO criteria)
- Centre-involved DME confirmed on SD-OCT (central subfield thickness ≥300 µm or presence of intraretinal cysts within central 1 mm)
- Treatment-naïve or previously treated DME (minimum 3-month washout from anti-VEGF or laser)
- Clear ocular media permitting high-quality OCT imaging
- Willingness to undergo comprehensive systemic evaluation

**Exclusion Criteria:**

- Other retinal vascular diseases (retinal vein occlusion, retinal arterial occlusion)
- Age-related macular degeneration
- Uveitic macular edema
- High myopia (spherical equivalent >-6.0 D)
- Significant media opacity (cataract grade ≥NO2/NC2, corneal opacity)
- Prior vitreoretinal surgery
- Uncontrolled glaucoma (IOP >21 mmHg)
- Concurrent severe systemic illness affecting study participation

**Clinical Phenotyping Protocol**

All participants underwent comprehensive clinical phenotyping across four primary domains:

**1. Glyco-Inflammatory Domain**

- HbA1c (HPLC method, NGSP-certified)
- Fasting plasma glucose and random blood glucose
- High-sensitivity C-reactive protein (hs-CRP) where available
- Duration of diabetes and current medication regimen

**2. Metabolic-Vasculopathic Domain**

- Blood pressure (average of three readings, JNC-8 protocol)
- Lipid profile: Total cholesterol, LDL, HDL, triglycerides
- Non-HDL cholesterol and atherogenic index of plasma (AIP): log(triglycerides/HDL)

**3. Renal Microangiopathy Domain**

- Serum creatinine and eGFR (CKD-EPI equation)
- Urine microalbumin/creatinine ratio (spot sample)
- Albuminuria classification: normal (<30 mg/g), microalbuminuria (30–300 mg/g), macroalbuminuria (>300 mg/g)

**4. Lifestyle and Anthropometric Variables**

- BMI using WHO Asia-Pacific criteria
- Smoking status and pack-years calculation
- Physical activity level (self-reported)

**Ophthalmic Examination**

Each participant underwent comprehensive ophthalmic evaluation including BCVA (ETDRS protocol, logMAR), contrast sensitivity (Pelli-Robson chart), slit-lamp biomicroscopy, dilated fundus examination, fundus photography (ETDRS 7-standard fields), and diabetic retinopathy severity grading (ETDRS classification).

**Structural Imaging Protocol**

High-resolution macular imaging was performed using Heidelberg Spectralis or Zeiss Cirrus HD-OCT. Structural endpoints included Central Macular Thickness (CMT), Cystoid Morphology Analysis, DRIL Extent (horizontal measurement in µm), ELM/EZ Integrity (graded 0–3), Subfoveal Choroidal Thickness (EDI scans), and presence of Subretinal Fluid.

**Statistical Analysis**

All analyses were performed using SPSS version 26.0 and R version 4.2. Descriptive statistics, Pearson/Spearman correlations, multivariate regression with interaction modelling, hierarchical cluster analysis, and systems-biomarker model construction with bootstrapping (1000 iterations) were performed. Statistical significance was set at $p < 0.05$ (two-tailed) with Bonferroni correction for multiple comparisons.

## Results

**Study Population Characteristics**

A total of 186 eyes from 124 patients with DME were enrolled. Baseline demographic, systemic, and ocular characteristics are presented in [Table 1 and 2].

**Table 1: Baseline demographic and systemic characteristics**

| Parameter | Value |
|---|---|
| Age (years) | 58.3 ± 8.7 |
| Male sex, n (%) | 71 (57.3%) |
| Duration of diabetes (years) | 11.2 ± 5.6 |
| HbA1c (%) | 8.6 ± 1.2 |
| Fasting plasma glucose (mg/dL) | 156 ± 42 |
| hs-CRP (mg/L) | 4.8 ± 2.3 |
| Systolic BP (mmHg) | 142 ± 18 |
| Diastolic BP (mmHg) | 86 ± 11 |
| Hypertension, n (%) | 89 (71.8%) |
| Duration of hypertension (years) | 6.4 ± 4.2 |
| Total cholesterol (mg/dL) | 198 ± 46 |
| LDL cholesterol (mg/dL) | 118 ± 38 |
| HDL cholesterol (mg/dL) | 42 ± 9 |
| Triglycerides (mg/dL) | 182 ± 68 |
| Atherogenic index of plasma | 0.64 ± 0.22 |
| Dyslipidemia, n (%) | 79 (63.7%) |
| Serum creatinine (mg/dL) | 1.1 ± 0.4 |
| eGFR (mL/min/1.73m²) | 76 ± 22 |
| Microalbuminuria, n (%) | 57 (46.0%) |
| Macroalbuminuria, n (%) | 18 (14.5%) |
| BMI (kg/m²) | 26.8 ± 3.9 |
| Current/former smokers, n (%) | 32 (25.8%) |
| Smoking pack-years | 8.6 ± 6.2 |

**Table 2: Baseline ocular and structural imaging characteristics**

| Parameter | Value |
|---|---|
| BCVA (logMAR) | 0.48 ± 0.32 |
| Contrast sensitivity (log) | 1.35 ± 0.28 |
| DR severity: Mild NPDR, n (%) | 34 (27.4%) |
| DR severity: Moderate NPDR, n (%) | 52 (41.9%) |
| DR severity: Severe NPDR, n (%) | 28 (22.6%) |
| DR severity: PDR, n (%) | 10 (8.1%) |
| Central macular thickness (µm) | 418 ± 112 |
| DRIL extent (µm) | 562 ± 384 |
| ELM/EZ: Grade 0 – intact, n (%) | 28 (22.6%) |
| ELM/EZ: Grade 1 – focal disruption, n (%) | 46 (37.1%) |
| ELM/EZ: Grade 2 – extensive disruption, n (%) | 34 (27.4%) |
| ELM/EZ: Grade 3 – complete loss, n (%) | 16 (12.9%) |
| Number of cysts | 8.2 ± 4.6 |
| Mean cyst diameter (µm) | 186 ± 74 |
| Subfoveal choroidal thickness (µm) | 242 ± 68 |
| Subretinal fluid, n (%) | 22 (17.7%) |
| Composite OCT severity score | 2.48 ± 1.12 |

**Correlation Analysis: Clinical Domains vs Structural Severity:** HbA1c demonstrated strong positive correlations with multiple structural severity markers: DRIL extent (r = 0.622, p < 0.001), ELM/EZ disruption grade (r = 0.548, p < 0.001), CMT (r = 0.387, p < 0.001), and composite OCT severity score (r = 0.614, p < 0.001). Duration of diabetes showed moderate correlations with DRIL extent (r = 0.441), ELM/EZ disruption (r = 0.398), and choroidal thinning (r = -0.352). hs-CRP (n = 86 patients) correlated with diffuse cystoid pattern (OR = 2.8, 95% CI: 1.4–5.6), number of cysts (r = 0.412), and CMT (r = 0.368).

Systolic blood pressure demonstrated significant associations with CMT (r = 0.411), chronic cystoid edema (OR = 3.2, 95% CI: 1.6–6.4), and composite severity score (r = 0.368). LDL cholesterol showed strong associations with hard exudate burden (r = 0.586, p < 0.001), outer retinal involvement (OR = 2.4), and subretinal fluid (OR = 2.1).

Urine microalbumin/creatinine ratio demonstrated robust correlations with CMT (r = 0.468), DRIL extent (r = 0.512), diffuse edema pattern (OR = 4.2, 95% CI: 2.1–8.4), and composite severity score (r = 0.536). Presence of macroalbuminuria (n = 18) was associated with higher mean CMT (512 ± 96 vs 398 ± 108 µm, p < 0.001), greater DRIL extent (782 ± 312 vs 518 ± 374 µm, p = 0.002), and more severe ELM/EZ disruption (mean grade 2.1 vs 1.3, p = 0.004).

**Multivariate Regression Models**

**Table 3: Independent predictors of DRIL extent (μm)**

| Variable | β coefficient | 95% CI | p-value |
|---|---|---|---|
| HbA1c | 86.4 | 62.2–110.6 | < 0.001 |
| Microalbuminuria | 124.8 | 88.6–161.0 | < 0.001 |
| Duration of diabetes | 18.2 | 8.4–28.0 | < 0.001 |
| Systolic BP | 4.8 | 1.6–8.0 | 0.004 |
| Model $R^2 = 0.624$, adjusted $R^2 = 0.612$ | | | |

**Table 4: Independent predictors of ELM/EZ disruption grade**

| Variable | OR | 95% CI | p-value |
|---|---|---|---|
| HbA1c (per 1% increase) | 2.14 | 1.62–2.82 | < 0.001 |
| DRIL extent (per 100 μm) | 1.42 | 1.24–1.62 | < 0.001 |
| Duration of diabetes | 1.12 | 1.04–1.20 | 0.002 |
| eGFR (per 10 units decrease) | 1.28 | 1.08–1.52 | 0.005 |
| Pseudo $R^2$ (Nagelkerke) = 0.586 | | | |

**Table 5: Independent predictors of central macular thickness (μm)**

| Variable | β coefficient | 95% CI | p-value |
|---|---|---|---|
| Microalbuminuria | 88.4 | 56.2–120.6 | < 0.001 |
| Systolic BP | 2.8 | 1.2–4.4 | 0.001 |
| HbA1c | 24.6 | 10.8–38.4 | 0.001 |
| LDL cholesterol | 0.68 | 0.22–1.14 | 0.004 |
| hs-CRP | 12.4 | 4.6–20.2 | 0.002 |
| Model $R^2 = 0.548$, adjusted $R^2 = 0.532$ | | | |

**Composite Systems-Biomarker Panel:** A composite clinical phenotype panel was constructed incorporating HbA1c, urine microalbumin/creatinine ratio, LDL cholesterol, and sustained systolic blood pressure. A standardized composite systems-biomarker score was calculated as:

Systems Score = 0.35(Z-HbA1c) + 0.30(Z-microalbumin) + 0.20(Z-LDL) + 0.15(Z-SBP)

This four-biomarker panel explained 71.4% of variance in composite OCT severity score (adjusted $R^2 = 0.714$, $p < 0.001$), showed strong correlation with composite OCT severity ($r = 0.782$, $p < 0.001$), excellent discrimination for severe structural DME (AUC = 0.86, 95% CI: 0.80–0.92), and significant correlation with BCVA ($r = 0.624$, $p < 0.001$).

Interaction Effects

Significant multiplicative interactions were identified: HbA1c × microalbuminuria interaction significantly predicted DRIL extent beyond additive effects ($p = 0.008$); systolic BP × duration of hypertension interaction predicted choroidal thinning ($p = 0.012$); and LDL × HbA1c interaction predicted hard exudate burden ($p = 0.004$).

**Functional Correlations**

**Table 6: Structural predictors of BCVA (logMAR)**

| Variable | β coefficient | 95% CI | p-value |
|---|---|---|---|
| ELM/EZ disruption grade | 0.184 | 0.148–0.220 | < 0.001 |
| DRIL extent (per 100 μm) | 0.042 | 0.028–0.056 | < 0.001 |
| CMT (per 100 μm) | 0.028 | 0.012–0.044 | 0.001 |
| Contrast sensitivity | -0.268 | -0.342 to -0.194 | < 0.001 |
| Model $R^2 = 0.682$, adjusted $R^2 = 0.671$ | | | |

ELM/EZ disruption grade was the strongest predictor of visual dysfunction ($\beta = 0.184$, $p < 0.001$). Among clinical biomarkers, the systems-biomarker score independently predicted BCVA ($\beta = 0.112$ logMAR per 1-unit increase, $p < 0.001$) even after adjusting for structural OCT parameters. For contrast sensitivity, ELM/EZ integrity ($\beta = -0.142$), DRIL extent ($\beta = -0.00028$), and systems-biomarker score ($\beta = -0.086$) were significant predictors.

**Phenotype-Based Clustering:** Hierarchical cluster analysis identified three distinct DME clusters: Cluster 1 (n = 42, glyco-inflammatory dominant) with high HbA1c (mean 9.8%), elevated CRP, extensive DRIL (mean 782 μm), and severe ELM/EZ disruption; Cluster 2 (n = 48, metabolic-renal dominant) with moderate HbA1c (mean 7.8%), prominent microalbuminuria, hypertension, and diffuse cystoid edema; and Cluster 3 (n = 34, mixed mild-moderate) with better glycemic control (mean HbA1c 7.2%), dyslipidemia-predominant features, and preserved photoreceptor layers. These clusters demonstrated significantly different structural severity ($p < 0.001$) and functional outcomes ($p < 0.001$).

## Discussion

This study demonstrates that DME severity emerges from multidomain systemic interactions rather than isolated metabolic derangements. Our systems-biomarker framework, integrating glyco-inflammatory, metabolic-vascular, renal, and lifestyle phenotypes with advanced retinal imaging biomarkers, achieved 71.4% explanatory power for structural severity—substantially exceeding traditional single-marker approaches.

The robust correlation between HbA1c and DRIL extent ($r = 0.622$) reinforces that DME is fundamentally a neurodegenerative disorder. The strong association between

HbA1c and ELM/EZ disruption (r = 0.548) suggests that photoreceptor injury represents an endpoint of sustained metabolic stress. hs-CRP elevation correlated with diffuse cystoid patterns, supporting the role of systemic inflammation in blood-retinal barrier breakdown.

Sustained systolic hypertension emerged as an independent predictor of chronic cystoid edema (OR = 3.2) and increased CMT. The duration-dependent effect underscores the importance of early and sustained blood pressure control. LDL cholesterol's strong association with hard exudate burden (r = 0.586) reflects lipoprotein extravasation through compromised vascular barriers.

Microalbuminuria demonstrated the strongest independent association with diffuse edema patterns (OR = 4.2) and robust correlations with DRIL extent (r = 0.512) and CMT (r = 0.468). The eGFR inverse relationship with structural severity markers suggests that declining renal function parallels progressive retinal degeneration. These findings support routine renal function screening in DME patients.

ELM/EZ disruption emerged as the most powerful predictor of visual dysfunction (β = 0.184 for BCVA), surpassing CMT. This validates recent paradigm shifts recognizing that photoreceptor integrity determines visual potential more than fluid volume. DRIL extent also strongly predicted visual outcomes, consistent with meta-analyses demonstrating DRIL's prognostic value.

The four-biomarker panel (HbA1c, microalbuminuria, LDL, systolic BP) achieving 71.4% variance explanation represents a practical, implementable tool for DME risk stratification using readily available, inexpensive, and modifiable clinical tests.

**Limitations:** Limitations include the cross-sectional design precluding temporal causality assessment; single-center design from Kashmir, India, limiting generalizability; treatment heterogeneity despite washout periods; incomplete inflammatory panel (hs-CRP not universally measured); potential confounding by medications; and absence of genetic analysis.

## Conclusion

Diabetic macular edema severity arises from orchestrated interactions across multiple systemic domains—glyco-inflammatory, metabolic-vascular, renal microangiopathic, and lifestyle factors—rather than isolated hyperglycemia. This systems-biomarker analysis demonstrates that a composite clinical phenotype panel integrating HbA1c, microalbuminuria, LDL cholesterol, and systolic blood pressure explains 71.4% of structural severity variance.

Structural biomarkers, particularly DRIL extent and ELM/EZ integrity, serve as powerful integrative readouts of cumulative systemic insults and predict functional vision loss more accurately than central macular thickness. The identification of distinct clinical phenotype clusters suggests heterogeneous pathophysiologic mechanisms requiring personalized therapeutic approaches.

The transition from reductionist, single-biomarker approaches to integrative systems-biomarker profiling represents a paradigm shift toward precision medicine in diabetic retinal disease management.

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## Conflicts of interest

There are no conflicts of interest.

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