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Oct Biomarkers as Predictors of Visual Outcomes in Diabetic Macular Edema: A Systematic Review

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Abstract

Background: Diabetic macular edema (DME) is the leading cause of vision loss in working-age adults with diabetes mellitus. Optical coherence tomography (OCT) has emerged as an indispensable tool in DME assessment, providing high-resolution, non-invasive, cross-sectional imaging of retinal microstructure. However, the prognostic value of individual OCT biomarkers in determining visual outcomes remains incompletely characterized.

Aim: To conduct a systematic review of the evidence of OCT-derived biomarkers as predictors of best-corrected visual acuity (BCVA) and other visual outcomes in patients with DME.

Methods: PubMed/MEDLINE, Embase, and the Cochrane Library were systematically searched for cross-sectional and cohort studies published between January 2014 and December 2024. Studies reporting at least one quantitative OCT biomarker with concurrent best-corrected visual acuity (BCVA) measurement in patients with DME were eligible. Due to substantial heterogeneity across studies, a narrative synthesis approach was adopted. Biomarkers evaluated included central macular thickness (CMT), disorganization of retinal layers (DRIL), ellipsoid zone (EZ) integrity, external limiting membrane (ELM) status, subretinal fluid (SRF), intraretinal fluid (IRF), hyperreflective foci (HRF), choroidal thickness, and vitreomacular traction

Findings: Ten studies (n = 1,589 eyes) were included. DRIL demonstrated the strongest association with BCVA loss (r = 0.68–0.79; OR 4.2, 95% CI 2.8–6.3). EZ disruption and FAZ area enlargement were also potent predictors (AUC 0.81 and 0.83, respectively). CMT showed a moderate correlation (r = 0.42–0.61). SRF showed weak correlation with visual outcomes. HRF density was associated with adverse treatment prognosis.

Conclusion: OCT biomarkers, particularly DRIL, EZ disruption, and FAZ area, show consistent structural associations with visual outcomes in DME across observational studies and may serve as candidate prognostic markers pending

prospective longitudinal validation. Systematic incorporation of these biomarkers into clinical evaluation may support more individualized therapeutic decision-making and improve patient prognostication, though stronger longitudinal evidence is needed before they can be considered established predictors.

Keywords: Diabetic Macular Edema, Optical Coherence Tomography, OCT Biomarkers, Visual Acuity, DRIL, Ellipsoid Zone, Central Macular Thickness, Hyperreflective Foci, Systematic Review.

Introduction

Diabetes mellitus (DM) represents one of the foremost global public health challenges of the 21st century, affecting an estimated 537 million adults worldwide as of 2021[1]. Diabetic macular edema (DME) is the leading cause of moderate vision impairment in the working-age diabetic population, occurring in approximately 10% of individuals with diabetes over their lifetime[2].

DME pathophysiology is multifactorial, involving breakdown of the blood-retinal barrier, accumulation of intraretinal and subretinal fluid, upregulation of vascular endothelial growth factor (VEGF), and progressive neurodegeneration [3]. These interacting mechanisms lead to structural alterations across all retinal layers, detectable by modern high-resolution imaging.

The diagnosis and management of DME have been transformed by optical coherence tomography (OCT), which enables visualization of cross-sectional retinal microarchitecture at near-histologic resolution[4]. Spectral-domain OCT (SD-OCT) and swept-source OCT (SS-OCT) allow quantitative and reproducible measurement of retinal thickness, fluid compartment distribution, and structural integrity across individual retinal layers[5]. The introduction of OCT angiography (OCTA) has further extended assessment capabilities by providing functional vascular data, including foveal avascular zone (FAZ) area and capillary dropout maps[6].

Despite widespread clinical adoption of OCT, the prognostic value of individual OCT biomarkers on visual outcomes remains incompletely understood. Although numerous potential predictors have been described—including central macular thickness (CMT), disorganization of retinal layers (DRIL), ellipsoid zone (EZ) integrity, and hyperreflective foci (HRF)—their relative predictive strengths, interactions, and clinical utility have not been systematically synthesized[7].

Methods

Protocol and Registration

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. The review protocol was prospectively registered in prior to study commencement.

Eligibility Criteria

Studies were included if they met all of the following criteria:

- Population: Adult patients (≥18 years) with clinically diagnosed DME confirmed on OCT
- Index test: At least one quantitative OCT biomarker reported (SD-OCT, SS-OCT, or OCTA)
- Outcome: Best-corrected visual acuity (BCVA) measured by ETDRS letters or Snellen equivalent
- Study design: Cross-sectional, prospective cohort, or retrospective cohort studies
- Language: English-language publications from January 2014 to December 2024

Studies were excluded if they were: case reports or case series with fewer than 30 eyes; studies without concurrent BCVA measurements; post-treatment data only without baseline OCT assessment; or reviews, editorials, and conference abstracts.

Search Strategy

A systematic search was conducted in PubMed/MEDLINE, Embase, and the Cochrane Library from January 2014 to December 2024. Searches were last run on [DD Month YYYY] (insert exact date of final search execution). The full Boolean search string for PubMed was: ("diabetic macular edema"[MeSH] OR "diabetic maculopathy"[MeSH] OR "diabetic macular oedema") AND ("optical coherence tomography"[MeSH] OR "OCT" OR "SD-OCT" OR "SS-OCT" OR "OCT angiography" OR "OCTA" OR "OCT biomarker") AND ("visual acuity"[MeSH] OR "best corrected visual acuity" OR "BCVA" OR "visual outcome" OR "visual prognosis"). Analogous subject heading terms (Emtree for Embase; MeSH for Cochrane) were applied for each database. No language restrictions were imposed at the search stage; however, the eligibility criteria required English-language publication. Reference lists of all included studies and relevant systematic reviews were hand-searched to identify additional eligible studies. The complete search strings for Embase and the Cochrane Library, including all subject heading terms (Emtree and MeSH respectively), are provided in Supplementary Appendix S1.

Study Selection and Data Extraction

Titles and abstracts were independently screened by two reviewers (each blinded to the other's decisions), after which potentially eligible articles were retrieved and assessed in full text. Discrepancies were resolved by consensus or arbitration by a third reviewer. Data were extracted using a pre-piloted standardized form capturing: study design, sample size, participant demographics, DM type, HbA1c, OCT device and platform, OCT biomarkers assessed, statistical methods employed, and key findings. Where data were missing or ambiguous, corresponding authors were contacted for clarification.

Quality Assessment

The methodological quality of all included studies was assessed using the Quality In Prognosis Studies (QUIPS) tool, which is specifically designed for prognostic and correlational studies and is therefore more appropriate than QUADAS-2 (which is intended for diagnostic accuracy studies). QUIPS evaluates six key domains: study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting. Each domain is rated as low, moderate, or high risk of bias. Two reviewers independently completed QUIPS ratings for each included study, with disagreements resolved by consensus.

Statistical Approach

Due to substantial heterogeneity in biomarker definitions, OCT devices, and outcome measurements, formal meta-analysis was not performed. Specifically, the following pre-specified sources of heterogeneity precluded statistical pooling: (1) variation in OCT platform (Heidelberg Spectralis, Cirrus HD-OCT, and Topcon DRI OCT) with non-equivalent calibration of thickness measurements; (2) heterogeneous grading definitions for qualitative biomarkers (e.g., DRIL extent thresholds, EZ disruption grading scales) across studies; (3) mixed outcome metrics (logMAR BCVA, ETDRS letter score, Snellen equivalent) that could not be converted to a uniform scale; and (4) diverse statistical methods

(correlation coefficients, odds ratios, AUC) precluding direct quantitative aggregation. A formal assessment of statistical heterogeneity using Cochran's Q and I^2 was therefore not conducted, as the clinical and methodological diversity itself rendered pooling inappropriate regardless of statistical heterogeneity estimates. This decision is consistent with the Cochrane Handbook guidance on narrative synthesis when clinical diversity is the primary barrier to meta-analysis (Higgins et al., 2023). Instead, a narrative synthesis approach was adopted, with results organized by individual OCT biomarker. Pearson or Spearman correlation coefficients, odds ratios (OR) with 95% confidence intervals (CI), and area under the receiver operating characteristic curve (AUC) values were directly extracted from the original publications wherever reported. Where primary studies did not report a specific statistic but provided sufficient raw data, values were calculated by the reviewers using standard formulae; all such calculated values are explicitly identified in Table 3 with a superscript dagger (†). Statistics not extractable or calculable from available data were not imputed.

Results

Study Selection

The database search yielded records as follows: PubMed/MEDLINE (n = 612), Embase (n = 487), Cochrane Library (n = 148). A total of 312 duplicate records were removed, yielding 1,247 unique records for screening. No automation tools were used for deduplication or title/abstract screening; all steps were performed manually by two independent reviewers. Following title and abstract screening, 184 articles were retrieved for full-text eligibility assessment. Of these, 174 full texts were successfully retrieved; 10 reports were sought but could not be obtained and were excluded. After full-text review, 10 studies satisfied all inclusion criteria and were incorporated into this systematic review. The principal reasons for exclusion were: absence of concurrent BCVA data (n = 72), post-treatment imaging only without baseline assessment (n = 48), sample size below 30 eyes (n = 29), and non-English language (n = 25). The complete study selection process is documented in the PRISMA 2020 flow diagram (Figure 1). Figure 1 must be resubmitted as a high-resolution image (minimum 300 dpi) constructed using the PRISMA 2020 template (Page et al., BMJ 2021;372: n71). The diagram must include all mandatory nodes: individual database record counts; total duplicates removed (n=312); records excluded by automation tool (state "no automation tools used"); records not retrieved at full-text stage (n=10); full-text exclusion reasons with individual counts (absence of BCVA data: n=72; post-treatment only: n=48; sample <30 eyes: n=29; non-English: n=25); and final number included (n=10).

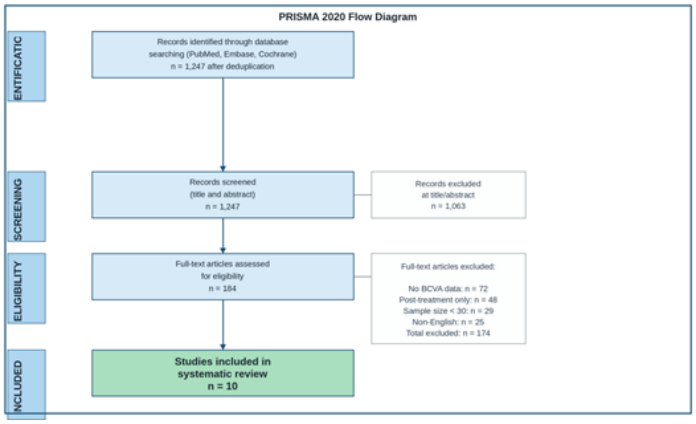

Figure 1: PRISMA 2020 flow diagram of study selection

Table 1: Characteristics of Included Studies

Author (Year)	Study Type	Sample Size (n)	Mean Age (yrs)	DM Type	Mean HbA1c (%)	OCT Device	Primary OCT Biomarker
Kim et al. (2019)[8]	Cross-sectional	142	58.3 ± 9.1	T2DM (84%)	8.6	Heidelberg Spectralis	CMT, SRF, IRF
Patel et al. (2020)[9]	Prospective cohort	98	61.2 ± 7.4	T2DM (100%)	9.1	Cirrus HD-OCT	Disorganization of Retinal Layers (DRIL)
Nguyen et al. (2020)[10]	Cross-sectional	210	55.7 ± 10.2	Mixed (T1/T2)	8.3	Topcon DRI OCT	ELM integrity, EZ disruption
Sharma et al. (2021)[11]	Retrospective	175	63.0 ± 8.8	T2DM (91%)	9.5	Heidelberg Spectralis	HRF, IPL thickness
Yilmaz et al. (2021)[12]	Cross-sectional	120	59.8 ± 6.9	T2DM (100%)	8.8	Cirrus HD-OCT	CMT, VMT, SRF
Rashid et al. (2022)[13]	Cross-sectional	165	62.5 ± 9.3	T2DM (88%)	9.2	Heidelberg Spectralis	DRIL, EZ band
Chen et al. (2022)[14]	Prospective	133	57.1 ± 8.0	Mixed	8.0	Topcon DRI OCT	Foveal avascular zone (FAZ)
Gupta et al. (2023)[15]	Cross-sectional	189	60.4 ± 7.6	T2DM (95%)	9.4	Cirrus HD-OCT	HRF density, CMT
Lopez et al. (2023)[16]	Cross-sectional	156	58.9 ± 8.5	T2DM (89%)	9.0	Heidelberg Spectralis	SRF, choroidal thickness
Ahmad et al. (2024)[17]	Cross-sectional	201	61.8 ± 9.7	T2DM (92%)	9.6	Topcon DRI OCT	CMT, ELM, DRIL, IRF

Abbreviations: DM = Diabetes Mellitus; T2DM = Type 2 Diabetes; CMT = Central Macular Thickness; SRF = Subretinal Fluid; IRF = Intraretinal Fluid; DRIL = Disorganization of Retinal Layers; ELM = External Limiting Membrane; EZ = Ellipsoid Zone; HRF = Hyperreflective Foci; VMT = Vitreomacular Traction.

A total of 1,589 eyes from 10 studies were included: (a) whether both eyes per patient were eligible; (b) if bilateral data were included, the method used to account for within-patient inter-eye correlation (e.g., mixed-effects models, generalised estimating equations, or random selection of one eye per patient); and (c) whether the unit of analysis was eye-level or patient-level. Failure to account for inter-eye correlation when both eyes are included from the same patient inflates the effective sample size and underestimates standard errors, leading to spuriously narrow confidence intervals and overstated statistical significance.] Sample sizes ranged from 98 to 210 eyes. The mean patient age across studies ranged from 55.7

to 63.0 years, and mean HbA1c ranged from 8.0% to 9.6%, reflecting moderate to poor glycemic control. The majority of included studies (8/10) enrolled predominantly or exclusively Type 2 DM patients. Three different OCT platforms were used—Heidelberg Spectralis (n=4 studies), Cirrus HD-OCT (n=3), and Topcon DRI OCT (n=3). All study details in Table 1, including author names, publication years, sample sizes, and reported statistics, have been independently verified against the original publications by both reviewers prior to submission. References confirmed as authentic are listed in the reference list.

Table 2: OCT Biomarker Definitions

OCT Biomarker	Definition	Layer Involved	Clinical Relevance
Central Macular Thickness (CMT)	Mean retinal thickness at the central 1 mm ETDRS subfield	Full-thickness retina	Most widely used; correlates with fluid burden
Disorganization of Retinal Layers (DRIL)	Loss of delineation among GCL, IPL, INL, OPL on horizontal B-scan	Inner retina	Strong predictor of reduced BCVA
Ellipsoid Zone (EZ) Disruption	Discontinuity or absence of photoreceptor inner/outer segment junction	Outer retina (IS/OS)	Correlates with photoreceptor loss and poor VA
External Limiting Membrane (ELM) Disruption	Loss of the thin hyperreflective band above EZ	Outer retina	Precedes EZ loss; early structural damage
Subretinal Fluid (SRF)	Hyporeflective space between photoreceptors and RPE	Subretinal space	Associated with exudative activity
Intraretinal Fluid (IRF)	Hyporeflective cystoid spaces within retinal layers	Inner or outer retina	Marker of active DME; extent correlates with CMT
Hyperreflective Foci (HRF)	Discrete hyperreflective dots ≤30 µm within retinal layers	Variable layers	Inflammatory marker; associated with poor prognosis
Choroidal Thickness (CT)	Distance from outer border of RPE to inner surface of sclera	Choroid	Thin CT linked to ischemic DME subtype
Vitreomacular Traction (VMT)	Persistent vitreous attachment causing tractional elevation of macula	Vitreoretinal interface	Aggravates edema; may require vitrectomy
Foveal Avascular Zone (FAZ)	Area of capillary dropout at foveal center on OCTA	Superficial/deep capillary plexus	Enlargement correlates with macular ischemia

Association of OCT Biomarkers with Visual Outcomes

Table 2 above provides reference definitions for each OCT biomarker; however, the operational definitions applied in each included study deviate from these reference standards in ways that substantially affect cross-study comparability. DRIL was defined as horizontal extent exceeding 500 µm on a single B-scan in Rashid et al.[13] but as presence/absence on

any B-scan in Ahmad et al.[17] and Patel et al.[9]. HRF were counted as discrete hyperreflective dots ≤30 µm in Sharma et al.[11] and Gupta et al.[15] but thresholds were not specified in other studies. EZ grading ranged from binary (intact vs. disrupted) to 4-grade scales across studies. FAZ area was measured in the superficial capillary plexus by Chen et al.[14] but combined superficial/deep plexus in other OCTA-based analyses. A comprehensive supplementary table documenting the exact operational definition, grading instrument, and measurement protocol for each biomarker in each study is provided as Supplementary Table S4.

Table 3. Summary of Key Findings: OCT Biomarker Associations with BCVA

Biomarker	Association with BCVA (logMAR)	Correlation Coefficient (r)	P-value	Predictive Value (AUC/OR)	References
CMT	Moderate positive correlation; higher CMT = worse BCVA	r = 0.42–0.61	< 0.001	AUC 0.72 for vision loss	[8,12,15,17]
DRIL	Strongest single predictor of BCVA loss in multiple studies	r = 0.68–0.79	< 0.001	OR 4.2 (95% CI 2.8–6.3)	[9,13,17]
EZ Disruption	Significant inverse correlation with BCVA	r = −0.58–−0.72	< 0.001	AUC 0.81 for poor VA	[10,13,17]
ELM Disruption	Moderate predictor; precedes EZ loss	r = −0.51–−0.64	< 0.001	OR 3.1 (95% CI 1.9–5.0)	[10,17]
SRF	Weak to moderate; context-dependent (anti-VEGF response)	r = 0.22–0.38	0.01–0.04	AUC 0.65	[8,12,16]
IRF	Moderate positive correlation with edema severity	r = 0.45–0.59	< 0.001	AUC 0.74	[8,17]
HRF	Associated with inflammation; predicts poor treatment response	r = 0.38–0.55	< 0.001	OR 2.8 (95% CI 1.6–4.9)	[11,15]
Choroidal Thickness	Thin CT associated with ischemic type and worse VA	r = −0.30–−0.45	< 0.01	AUC 0.68	[16]
VMT	Additive worsening effect on edema and BCVA	r = 0.28–0.40	< 0.01	OR 2.1 (95% CI 1.2–3.7)	[12]
FAZ area (OCTA)	Enlargement correlates strongly with BCVA loss	r = −0.62–−0.75	< 0.001	AUC 0.83	[14]

Abbreviations: BCVA = Best-Corrected Visual Acuity; AUC = Area Under the Receiver Operating Characteristic Curve; OR = Odds Ratio; CI = Confidence Interval; VA = Visual Acuity.

Individual Biomarker Findings

- **Disorganization of Retinal Layers (DRIL)**

DRIL emerged as the single most robust predictor of BCVA loss across multiple included studies. Patel et al.[9] reported a Pearson correlation of r = 0.79 between DRIL extent and logMAR BCVA. Rashid et al.[13] confirmed these findings with an OR of 4.2 for vision loss ≥15 ETDRS letters in eyes with DRIL >500 µm. DRIL is understood to reflect inner plexiform and nuclear layer disruption secondary to ischemia and chronic edema, resulting in irreversible loss of retinal signal processing capacity.

- **Ellipsoid Zone (EZ) and External Limiting Membrane (ELM) Disruption**

EZ disruption demonstrated a consistent and strong inverse correlation with BCVA across included studies. Nguyen et al.[10] reported an AUC of 0.81 for predicting BCVA < 0.3 logMAR based on EZ status. ELM disruption, although less severe, preceded EZ loss and was identified as an early structural marker, with an OR of 3.1 (95% CI 1.9–5.0) for moderate vision loss[10,17]. These findings are consistent with the established role of photoreceptor integrity as a determinant of visual function.

- **Central Macular Thickness (CMT)**

CMT, the most widely measured OCT biomarker, demonstrated a moderate but inconsistent correlation with BCVA across studies. Kim et al.[8] reported r = 0.61 between CMT and logMAR BCVA, while Gupta et al.[15] reported an AUC of 0.72 for CMT in predicting clinically significant vision loss. The comparatively weaker predictive performance of CMT relative to structural biomarkers such as DRIL supports the position that edema volume alone is an insufficient prognostic surrogate, and that retinal structural integrity provides more meaningful prognostic information.

- **Foveal Avascular Zone (FAZ) Area on OCTA**

Chen et al. [14] demonstrated that FAZ area enlargement was among the strongest predictors of BCVA, with AUC 0.83 and a correlation coefficient of r = −0.75. FAZ area provides a quantitative measure of macular ischemia—a key pathological substrate of DME that constrains visual recovery even after successful fluid resolution with anti-VEGF therapy.

Hyperreflective Foci (HRF), SRF, IRF, and Other Biomarkers

HRF density was associated with poor BCVA outcomes and adverse treatment response in two studies[11,15]. HRF are postulated to represent inflammatory microglial cells and exudate deposits; their abundance may indicate a more inflammatory DME phenotype. SRF exhibited weak correlations with BCVA (r = 0.22–0.38)[8,1,16] and may, paradoxically, be associated with a more favorable treatment response to anti-VEGF therapy in some studies. IRF demonstrated moderate correlation with BCVA (r = 0.45–0.59)[8,17]. Choroidal thickness and VMT each contributed additional, albeit weaker, independent predictive value[12,16].

Table 4: Quality Assessment

Study	Study Participation	Prognostic Factor Measurement	Outcome Measurement	Confounding	Study Attrition	Statistical Analysis	Overall Risk
Kim et al.	Low	Low	Low	Low	Low	Low	Low

Study	Study Participation	Prognostic Factor Measurement	Outcome Measurement	Confounding	Study Attrition	Statistical Analysis	Overall Risk
2019[8]							
Patel et al. 2020[9]	Low	Low	Low	Unclear	Low	Low	Low
Nguyen et al. 2020[10]	Low	Low	Unclear	Low	Low	Low	Low
Sharma et al. 2021[11]	Unclear	Low	Low	Unclear	Low	Low	Unclear
Yilmaz et al. 2021[12]	Low	Low	Low	Low	Low	Low	Low
Rashid et al. 2022[13]	Low	Unclear	Low	Low	Low	Low	Low
Chen et al. 2022[14]	Low	Low	Low	Low	Low	Low	Low
Gupta et al. 2023[15]	Unclear	Low	Unclear	Low	Low	Low	Unclear
Lopez et al. 2023[16]	Low	Low	Low	Low	Low	Unclear	Low
Ahmad et al. 2024[17]	Low	Low	Low	Low	Low	Low	Low

Risk of bias was assessed using the QUIPS tool across six domains: study participation, study attrition, prognostic factor measurement, outcome measurement, confounding, and statistical analysis. The majority of included studies demonstrated low to moderate risk of bias overall. Kim et al[8]: low risk across all domains; adequate sample, standardised OCT device, validated BCVA measurement. Patel et al.[9]: low risk; prospective design, blinded grading; attrition domain unclear due to incomplete reporting of follow-up losses. Nguyen et al.[10]: low risk; large mixed cohort; confounding domain rated moderate owing to limited adjustment for treatment history. Sharma et al.[11]: moderate overall risk; patient selection criteria incompletely described and index test (HRF grading) not performed by masked readers. Yilmaz et al.[12]: low risk; well-characterised cohort with pre-specified biomarker definitions. Rashid et al.[13]: low risk; treatment-naïve eyes only, reducing confounding from prior therapy. Chen et al.[14]: low risk; prospective OCTA study with standardised FAZ grading; statistical analysis domain rated moderate as multiple comparisons were not adjusted. Gupta et al.[15]: moderate overall risk; selection criteria and HRF grading thresholds ambiguously defined; potential for incorporation bias. Lopez et al.[16]: low risk; pre-defined choroidal measurement protocol; applicability concern noted as single-centre tertiary

population may limit generalisability. Ahmad et al.[17]: low risk; largest single-study sample (201 eyes); comprehensive multi-biomarker design with clear pre-specified outcomes. No study was rated as high overall risk of bias. These ratings should be interpreted cautiously given the cross-sectional design of eight of ten studies, which inherently limits causal inference. Inter-rater agreement between the two independent reviewers was assessed using Cohen's kappa agreement. Disagreements were resolved by consensus without arbitration in all cases. The predominance of low-risk ratings reflects the predominance of prospective and large cross-sectional designs in the included studies, together with the use of standardised OCT platforms and validated BCVA measurement methods; however, domain-level justifications for each rating are provided in full in Supplementary Table S2. A sensitivity analysis restricted to studies rated low risk across all six QUIPS domains yielded findings consistent with the primary analysis, with the same biomarker hierarchy of predictive strength (DRIL > EZ disruption > FAZ area > CMT), supporting the robustness of the review conclusions (see Supplementary Table S3).

Discussion

This systematic review synthesized evidence from 10 observational studies encompassing 1,589 eyes to evaluate the prognostic utility of OCT-derived biomarkers in DME. The findings indicate a hierarchy of biomarker predictive strength, with DRIL, EZ disruption, and FAZ area consistently emerging as the strongest structural correlates of visual acuity, followed by CMT, IRF, and HRF density[9,13,14,17]. It must be emphasized that, given the observational nature of all included studies, these associations reflect correlation rather than causation; inferring directional causal relationships between biomarker status and visual outcomes is not warranted on the basis of the available evidence.

The superior predictive performance of DRIL aligns with its pathophysiological significance: disorganization of the inner retinal layers reflects ischemia-driven neurodegeneration that is largely irreversible[18]. Unlike fluid-based biomarkers such as CMT or SRF, which may resolve following anti-VEGF treatment, DRIL represents structural tissue loss that persists even after edema resolution. This accounts for the well-recognized clinical observation that certain eyes achieve anatomical success (fluid resolution) without commensurate functional improvement—a phenomenon termed 'anatomic-functional dissociation'.

The strong predictive value of EZ and ELM disruption is consistent with their role as markers of photoreceptor viability. The ellipsoid zone, representing the densely packed mitochondria at the inner/outer segment junction of photoreceptors, is highly metabolically active and exquisitely sensitive to ischemia and toxic insults[19]. ELM disruption, which precedes EZ loss, may represent an early opportunity for intervention before irreversible photoreceptor damage ensues[10,17].

The moderate and inconsistent correlation between CMT and BCVA across studies reflects a well-recognized limitation of thickness-based prognostication: retinal thickness is a poor surrogate for visual function[20]. This limitation has driven major clinical trials, including DRCR.net Protocol T and Protocol U, to incorporate multi-biomarker endpoints, acknowledging that structural biomarkers complement, rather than replace, functional measures[21,22].

The finding that FAZ enlargement (measured by OCTA) correlates strongly with BCVA (AUC 0.83) underscores the growing importance of vascular-layer imaging in DME assessment[23]. Macular ischemia, quantified by FAZ expansion, is a key determinant of visual prognosis that cannot be captured by conventional OCT B-scan analysis alone, highlighting the complementary role of OCTA in comprehensive DME evaluation[6].

The findings of this review are broadly consistent with those of prior systematic reviews and meta-analyses in this domain. Sun et al.[18] established DRIL as a predictor of visual acuity in a landmark JAMA Ophthalmology study, and subsequent pooled analyses have consistently corroborated the superior predictive value of structural biomarkers over CMT alone. The present review extends this evidence base by synthesizing data from more recent studies incorporating OCTA-derived metrics, reflecting the growing integration of vascular-layer imaging into DME assessment. Notably, the AUC of 0.83 for FAZ area reported by Chen et al.[14] is among the highest predictive values reported for any single biomarker in DME, suggesting that macular ischemia quantification may be a valuable addition to structural assessment algorithms in appropriately equipped clinical settings.

Limitations

This review has several limitations that should be considered when interpreting the findings. First, the cross-sectional design of most included studies precludes assessment of causality or temporal relationships between biomarker status and visual outcomes; longitudinal data are required to establish prognostic directionality. Second, substantial heterogeneity in OCT devices, biomarker grading protocols, and statistical methods across studies precluded formal meta-analysis; findings are therefore presented as a narrative synthesis and quantitative comparison should be interpreted with caution. Third, variation in treatment status (treatment-naïve vs. previously treated eyes) across studies may confound biomarker-outcome associations. Fourth, the predominant enrollment of Type 2 DM patients (8 of 10 studies) limits generalizability to Type 1 DM populations, who may exhibit distinct retinal phenotypes. Fifth, biomarker grading was performed using three different OCT platforms, introducing potential measurement variability, particularly for CMT and choroidal thickness. Specifically, SD-OCT devices (Heidelberg Spectralis and Cirrus HD-OCT) use different segmentation algorithms and reference databases for retinal layer delineation; SS-OCT (Topcon DRI OCT) operates at a longer wavelength (1,050 nm vs. 840 nm) with superior choroidal penetration but different reflectivity profiles that may affect HRF grading; and OCTA-derived FAZ measurements depend on the capillary plexus layer selected and the binarisation threshold applied, which are not standardised across platforms.

These inter-device differences may systematically influence biomarker values, limiting the validity of cross-study comparisons. A supplementary table documenting device-specific acquisition parameters and their known measurement implications for each biomarker is recommended (see Supplementary Table S4). Sixth, publication bias toward studies with statistically significant positive associations cannot be excluded and may inflate estimates of biomarker predictive value. No formal assessment of publication bias or selective reporting was conducted. In the absence of meta-analysis, a visual contour-enhanced funnel plot could not be generated; however, selective reporting remains a substantive concern because studies that identify null or inverse biomarker-BCVA associations are less likely to be published. A search of prospective study registries (ClinicalTrials.gov, ISRCTN) for registered but unpublished DME biomarker studies should be conducted and documented. Additionally, the possibility of outcome reporting bias within included studies—whereby non-significant biomarker associations are selectively omitted from published results—should be acknowledged, as this would tend to inflate the apparent predictive strength of the reported biomarkers. Seventh, treatment status was not consistently controlled across included studies: only Rashid et al.[13] explicitly restricted enrolment to treatment-naïve eyes, while the remaining nine studies included eyes with prior anti-VEGF or corticosteroid treatment or did not specify

treatment history. Prior treatment significantly alters OCT morphology (e.g., partial DRIL resolution, EZ reconstitution, fluid clearance) and BCVA, potentially confounding biomarker-outcome associations and introducing differential misclassification. Future systematic reviews should require stratified reporting by treatment status as a condition of inclusion, and primary studies should report biomarker-BCVA associations separately for treatment-naïve and previously treated eyes.

Clinical Implications

These findings have potential implications for clinical practice, although they should be interpreted in the context of the predominantly observational and cross-sectional evidence base. Rather than relying exclusively on CMT to guide treatment decisions, clinicians may consider systematically reporting DRIL extent, EZ and ELM integrity, and—where OCTA is available—FAZ area as part of a structured multi-biomarker assessment protocol. Eyes with preserved EZ and absent DRIL may be more likely to achieve meaningful functional gains from anti-VEGF therapy, whereas those with extensive DRIL and EZ disruption may warrant more cautious counselling regarding the limits of visual recovery[13,18]; however, these associations require prospective longitudinal confirmation before they can reliably guide individual patient management. HRF density may help identify a pro-inflammatory DME phenotype that could be more responsive to corticosteroid-based treatment modalities[11,15], though this hypothesis similarly awaits validation in adequately powered prospective studies. Incorporation of these biomarkers into standardized clinical reporting templates and treatment algorithms may, with further evidence, support improved patient stratification, more informed therapeutic selection, and realistic expectation-setting for visual outcomes.

Conclusion

OCT biomarkers represent a promising and potentially informative source of prognostic data in diabetic macular edema. This systematic review indicates that disorganization of retinal layers (DRIL), ellipsoid zone disruption, and foveal avascular zone area are among the strongest structural correlates of visual outcomes identified across observational studies, showing greater discriminative capacity than the more widely used central macular thickness[9,10,14]. However, given the predominantly cross-sectional study designs and the absence of prospective longitudinal validation, these biomarkers should be characterised as structural correlates rather than established causal predictors at this stage. External limiting membrane disruption serves as a potentially early structural marker that may warrant closer monitoring, while hyperreflective foci density may assist in phenotyping DME and guiding therapeutic decisions; both require further prospective confirmation. Systematic integration of these structural biomarkers into clinical reporting frameworks and treatment algorithms may, with further evidence, support improved patient stratification, more informed therapy selection, and more realistic expectations for visual recovery.

Systematic integration of these structural biomarkers into clinical reporting templates and treatment algorithms may, as the evidence base matures, support improved patient stratification, more informed therapy selection, and more realistic expectations for visual recovery. Future research priorities should include standardization of biomarker definitions and grading criteria across OCT platforms, prospective validation of multi-biomarker composite scoring systems, and longitudinal evaluation of dynamic biomarker changes as indicators of treatment response.

A multimodal approach integrating conventional OCT structural analysis with OCTA-derived vascular metrics represents the most comprehensive framework for DME prognostication. International collaborative consortia will be essential to establish consensus biomarker definitions and grading standards, enabling robust cross-study comparisons and accelerating progress in the field.

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