

Predicting Visual Acuity Change by OCT and OCTA Biomarkers in Diabetic Macular Edema: A KINGFISHER Study Analysis

Michael Ip

MIp@doheny.org

Doheny Eye Institute

Mai Alhelaly

<https://orcid.org/0000-0003-0574-1660>

Alberto Quarta

G. d'Annunzio University of Chieti-Pescara- Depart <https://orcid.org/0000-0002-0818-6124>

Rouzbeh Abbasgholizadeh

Muneeswar Nittala

Doheny Eye Institute

Ceren Soylu

Kang Yeun Pak

Chang Ki Yoon

Seoul National University Hospital

Magdy Moussa

Tanta University, Egypt

Raiyna Rattu

Mohamed El-Bradey

Yu-Chien Chung

Fu Jen Catholic University Hospital <https://orcid.org/0000-0003-4745-8601>

Mamdouh Kabil Kabil

Shinichiro Chujo

Doheny Eye Institute

Hyun Duck Kwak

Swetha Bindu Velaga

<https://orcid.org/0000-0002-4637-6914>

Giulia Corradetti

Doheny Eye Institute

SriniVas Sadda

Doheny Eye Institute <https://orcid.org/0000-0002-4939-3306>

Article

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Abstract

Purpose

To evaluate baseline optical coherence tomography (OCT) and OCT angiography (OCTA) biomarkers that predict visual acuity (VA) outcomes in eyes with center-involved diabetic macular edema (CI-DME) treated with anti-vascular endothelial growth factor (anti-VEGF) therapy.

Methods

This post hoc analysis included 60 eyes with available OCTA data from the randomized phase 3 KINGFISHER trial (NCT03917472), which compared monthly aflibercept and brolucizumab for DME over 52 weeks. Pooled treatment-assignment baseline spectral-domain OCT and OCTA (Spectralis, Heidelberg Engineering) were analyzed for structural and vascular biomarkers. OCT metrics included central subfield thickness (CSFT), subretinal fluid (SRF), disorganization of retinal inner layers (DRIL), hyperreflective foci (HRF) volume, and disruption ratios of ellipsoid zone (EZ) and external limiting membrane (ELM). OCTA metrics from the superficial and deep vascular complexes (SVC, DVC) comprised perfusion density (PD), vessel length density (VLD), and fractal dimension (FD). Univariable and multivariable linear regression models were used to assess predictors of baseline VA, VA at week 52, and change in VA (Δ VA).

Results

Mean baseline VA was 62.9 ± 8.7 letters, improving to 75.4 ± 9.6 letters at week 52. In univariable analyses, greater CSFT and increased disruption of the EZ and ELM were associated with lower baseline VA; multivariable analysis identified CSFT as the sole independent predictor ($p = 0.014$; partial $R^2 = 0.158$). At week 52, univariable predictors of VA included EZ and ELM disruption, CSFT, and SVC PD and VLD; adjusted models demonstrated that both CSFT ($p = 0.045$; partial $R^2 = 0.078$) and SVC PD/VLD ($p = 0.022$; partial $R^2 = 0.062$) independently predicted VA outcomes. Higher baseline HRF volume was associated with reduced VA gain ($p < 0.001$; partial $R^2 = 0.104$), whereas preserved SVC perfusion and vascular density correlated with greater VA improvement.

Conclusions: Long-term visual outcomes after anti-VEGF therapy are strongly influenced by retinal microvasculature integrity and biomarkers of inflammatory burden. Outer retinal structural disruption limited visual recovery. Integrating OCT and OCTA biomarkers may enhance prognostic precision in DME management.

Introduction

Diabetic macular edema (DME) is a key reason for vision impairment in individuals with diabetes mellitus (DM). DME arises from disruption of the blood-retinal barrier, which impairs the regulation of fluid exchange between retinal vessels and neural tissue. This breakdown permits the accumulation of fluid

and lipids within the macula, resulting in retinal thickening and visual impairment.^{1,2} DME can occur at any stage of diabetic retinopathy (DR) and become particularly vision-threatening when the fovea is involved. Epidemiologic studies reported that approximately 29% of patients with type 1 diabetes and up to 25% of those with type 2 diabetes develop DME as their disease progresses.^{3,4}

Traditionally, clinical trials evaluating diabetic macular edema (DME) have primarily relied on retinal thickness parameters, most commonly central subfield thickness (CSFT), as key anatomical endpoints when assessing therapeutic efficacy.^{5,6} These metrics are easily acquired, but have demonstrated a moderate association with visual acuity (VA); eyes with comparable CSFT values may exhibit widely different levels of visual performance.^{7–9} This discrepancy highlights the complex and multifactorial nature of DME. Beyond retinal thickness, a range of structural and vascular features—including the integrity of the foveal outer retinal layers, the condition of the inner retinal layers, macular perfusion status, the chronicity of edema, and the presence of subfoveal hyperreflective foci (HRF) or hard exudates—have been implicated in visual impairment.^{10–21} Consequently, macular thickness is now recognized as an inadequate stand-alone predictor of functional outcomes in DME.

The evolution in optical coherence tomography (OCT) and OCT angiography (OCTA) has transformed the management of DME.^{22–28} These imaging technologies enabled high-resolution assessment of retinal microstructure and capillary networks, supporting the identification of quantitative imaging biomarkers that reflect disease severity and treatment response. OCT evolution has enabled detailed evaluation of retinal layer integrity, particularly the external limiting membrane (ELM) and the ellipsoid zone (EZ), both of which are increasingly regarded as structural biomarkers associated with visual outcomes in macular diseases, including DME.^{14,29,30} OCTA allows noninvasive visualization of retinal microvasculature and its metrics such as vessel density and foveal avascular zone size that have been linked to treatment response and visual prognosis.^{26,31–34} We hypothesize that integrating structural and vascular metrics can deepen understanding of DME pathophysiology, allow more individualized risk stratification, and guide therapeutic decision-making in clinical practice and research.

The KINGFISHER trial³⁵ (ClinicalTrials.gov Identifier: NCT03917472) was a multicenter, masked clinical study comparing monthly brolocizumab and aflibercept for DME over 52 weeks. Leveraging this well-characterized cohort, the present post hoc analysis aims to evaluate both baseline OCT and OCTA biomarkers as predictors of visual acuity outcomes in a subset of eyes with center-involved DME (CI-DME) undergoing anti-vascular endothelial growth factor (anti-VEGF) therapy.

Methods

Study Design

This post hoc analysis included baseline spectral-domain optical coherence tomography (SD-OCT) and corresponding optical coherence tomography angiography (OCTA) images from participants enrolled in the KINGFISHER clinical trial.³⁵ Due to the relatively small numbers from this subset of eyes from the

KINGFISHER trial, this analysis pooled the data from the brolucizumab and aflibercept treated eyes. All participants provided written informed consent before enrollment. The study protocol was approved by the relevant institutional review boards or ethics committees and adhered to the tenets of the Declaration of Helsinki as well as the Health Insurance Portability and Accountability Act (HIPAA).

Eligible participants were required to be ≥ 18 years of age and have a diagnosis of type 1 or type 2 DM with visual impairment due to CI-DME, defined as an Early Treatment Diabetic Retinopathy Study (ETDRS) best-corrected visual acuity (BCVA) score between 73 and 23 letters and a central subfield thickness (CSFT) ≥ 320 μm on SD-OCT at baseline.

Key exclusion criteria included prior anti-VEGF therapy in the study eye within 3 months, intravitreal corticosteroid injections (e.g., dexamethasone) within 6 months, fluocinolone acetonide at any time, or a history of focal or panretinal photocoagulation or vitreoretinal surgery in the study eye. Eyes with high-risk proliferative diabetic retinopathy (PDR), active intraocular inflammation or infection, uncontrolled glaucoma, vitreous hemorrhage, or any media opacity compromising image quality were also excluded.

For the present analysis, only baseline images acquired using the Heidelberg Spectralis SD-OCT device (Spectralis HRA+OCT, Heidelberg Engineering, Heidelberg, Germany) and with corresponding Spectralis OCTA images available were included, as OCTA imaging was not mandated by the original KINGFISHER study protocol and its acquisition was performed at the discretion of the investigator, with the OCTA device varying by study center.

SD- OCT image analysis

Macular cube scans covering a 20×20 -degree area (97 B-scan lines; 1024×496) centered on the fovea with average ART of 10 and image quality of 20 or more were evaluated. Only the study eye was included in the analysis. The central subfield (CSF) was defined as the innermost 1-mm-diameter circle of the ETDRS grid centered on the fovea. Central subfield macular thickness (CSFT) was obtained using the device's built-in segmentation software with manual correction as needed.

The presence of disorganization of the retinal inner layers (DRIL) was assessed within the CSF B-scans. DRIL was defined as an area where the boundaries between the ganglion cell layer, inner plexiform layer, inner nuclear layer, and outer plexiform layer could not be distinguished, according to the description by Sun et al.⁹ DRIL was evaluated regardless of concurrent retinal edema or intraretinal cysts. The presence of subretinal fluid (SRF) within the CSF area was also recorded.

Hyperreflective foci (HRF) quantification: The volume of HRF was quantified using a previously described automated method using deep learning model.^{36,37} In brief, volumetric OCT scans centered on the fovea were analyzed to identify HRF as discrete, hyperreflective lesions located between the internal limiting membrane and the retinal pigment epithelium on each B-scan. HRF were counted if it consisted of at least three contiguous pixels. Segmentation was performed using U-net based convolutional neural network. For each eye, the total number of HRF pixels segmented across all 97 B-scans was summed

and converted into volumetric units (voxels), which were then transformed into cubic millimeters (mm³). A two-dimensional projected density map of HRF was subsequently generated, and the standard ETDRS grid was overlaid to divide the macula into the CSF, inner ring, and outer ring. For the present analysis, only the HRF volume within the CSF was used.

EZ and ELM disruption ratio: The extent of ellipsoid zone (EZ) and external limiting membrane (ELM) disruption within the CSF was quantified using infrared (IR) images and B-scans, following an approach similar to that previously described for geographic atrophy studies with some modifications.³⁸ All analyses were performed at the Doheny Retinal Imaging Research Laboratory (DIRRL) by two independent, trained graders (RA and CS). EZ was defined as the second hyperreflective outer retinal band on OCT. The ELM was defined as a thin hyperreflective line located immediately above the EZ. Any visible EZ signal, regardless of thickness, was considered intact; the EZ was considered lost only when no portion of the band was discernible.

Graders reviewed each B-scan within the CSF and manually annotated areas of EZ loss using an edge-detection guided approach. Annotation began at the edge of intact EZ and continued until a clear loss of the EZ band was observed; annotation was paused, then resumed at the next segment of intact EZ. This process was repeated across all B-scans until the entire region of EZ loss within the CSF was mapped. The en face maps were used to confirm the continuity of the mapped EZ loss. An identical procedure was repeated separately to delineate areas of ELM loss.

ETDRS grid was overlaid on the annotated IR images and the total area of EZ loss and ELM loss within CSF, defined as the innermost 1-mm-diameter circle (area ~ 0.79 mm²), was calculated. The EZ disruption ratio was defined as the percentage of the CSF area showing EZ loss (EZ loss area ÷ CSF area × 100), and the ELM disruption ratio was calculated analogously as the percentage of the CSF area showing ELM loss.

OCTA image analysis

OCTA was performed using a spectral-domain OCTA system (Spectralis HRA+OCT; Heidelberg Engineering, Heidelberg, Germany) with a volume acquisition protocol of 512 × 496 A-scans covering a 20° × 20° field centered on the fovea. Raw OCTA data were exported and submitted to the DIRRL for masked analysis by certified OCTA graders.

En face OCTA slabs of the superficial vascular complex (SVC) and deep vascular complex (DVC) were generated using the device's built-in segmentation software with the manufacturer's default layer boundaries. Each scan was reviewed for segmentation accuracy, and any segmentation errors were manually corrected by the reading center before further analysis. The corrected SVC and DVC slabs were exported and analyzed using ImageJ software (National Institutes of Health, Bethesda, MD, USA).

Quantitative vascular metrics included perfusion density (PD), vessel length density (VLD), and fractal dimension (FD). Consistent with prior reports,^{39,40} PD was defined as the percentage of the area

occupied by perfused vasculature within the analyzed region, while VLD was defined as the total length of perfused vessels per unit area (mm^{-1}). PD was calculated after image binarization, and VLD after skeletonization of the vascular network. FD was derived for both the SVC and DVC using a box-counting method as previously described.^{32,41} Grayscale OCTA images were standardized and binarized in ImageJ, then analyzed with the Fractalyse plug-in (Université de Franche-Comté, France), which overlays a grid of squares on the skeletonized image to automatically compute the fractal dimension (Ds value). All measurements were obtained separately for the SVC and DVC. **See figure 1**

Data collection

Demographic and clinical data were retrieved from the KINGFISHER study database. Variables included treatment arm assignment, BCVA letter score at baseline and after 52 weeks of therapy, age, sex, duration of DM, and baseline diabetic retinopathy severity score (DRSS).

Statistical Analysis

Descriptive statistics were calculated for all baseline variables. Continuous variables are presented as mean $\pm$ standard deviation (SD) while categorical variables are reported as counts and percentages. Univariable models were first fit to identify predictors of VA at each time point, with estimates, standard errors, 95% confidence intervals (CIs), and coefficient of determination (R^2) reported. Subsequently, predictors that were statistically significant in univariable analysis or deemed clinically relevant were included in multivariable linear regression models to adjust for potential confounding. Given the high collinearity between perfusion density and vessel length density, we created a composite PD/VLD to be included in the multivariable models for W52 and change in VA (Δ VA). Model performance was summarized by the full model R^2 , and the relative contribution of individual predictors was quantified by their partial R^2 values. All statistical tests were two-sided, with $p < 0.05$ considered statistically significant. All statistical analyses were conducted using R version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline Characteristics

A total of 60 eyes were included in the analysis. The mean baseline VA was 62.85 ± 8.73 ETDRS letters, with mean CSFT of 472.83 ± 128.66 μm . At follow-up, mean VA was 75.38 ± 9.62 ETDRS letters at week 52. The mean age of participants was 61.02 ± 7.76 years, with a mean duration of diabetic retinopathy of 16.01 ± 21.76 years. **Table 1** summarizes the cohort descriptives. Among the 60 eyes included, SRF was present in 17 cases (28.3%) and absent in 43 cases (71.7%). DRIL was observed in only 2 eyes (3.3%), while 58 eyes (96.7%) did not exhibit DRIL at baseline. Regarding sex distribution, 27 (45.0%) were female and 33 (55.0%) male. Aflibercept arm included 27 eyes (45.0%) and Brolucizumab included 33 eyes (55.0%).

Baseline Predictors of Visual Acuity

On univariable analysis CSFT showed the strongest association (estimate -0.033 , $p < 0.001$, $R^2 = 0.229$), indicating a higher CSFT was associated with lower acuity. Outer retinal biomarkers were also significant, including EZ disruption ratio (estimate -0.199 , $p < 0.001$, $R^2 = 0.185$) and ELM disruption ratio (estimate -0.222 , $p = 0.003$, $R^2 = 0.138$), with a greater extent of EZ and ELM disruption both associated with worse acuity. In the multivariable model the full model explained 32% of the variance in baseline VA ($R^2 = 0.324$). CSFT remained an independent predictor ($p = 0.014$, partial $R^2 = 0.158$), while the associations with EZ disruption (partial $R^2 = 0.030$, $p = 0.423$) and ELM disruption (partial $R^2 = 0.004$, $p = 0.867$) were attenuated (**Tables 2,3**).

Predictors of Final Visual Acuity (Week 52)

On univariable analysis significant predictors of VA at week 52 included ELM disruption ratio ($p = 0.002$, $R^2 = 0.150$), EZ disruption ratio ($p = 0.004$, $R^2 = 0.136$), Superficial (sup) VLD ($p = 0.023$, $R^2 = 0.086$), PD sup ($p = 0.034$, $R^2 = 0.075$), and CSFT ($p = 0.044$, $R^2 = 0.068$). Age showed a trend toward significance ($p = 0.095$). In the multivariable model the full model explained 28% of the variance in VA at week 52 ($R^2 = 0.277$). CSFT ($p = 0.045$, partial $R^2 = 0.078$) and the PD/VLD sup composite measure ($p = 0.022$, partial $R^2 = 0.062$) remained independently significant (**Tables 4,5**).

Predictors of Change in Visual Acuity from baseline to week 52 (Δ VA)

On univariable analysis, several features correlated with VA improvement. HRF was negatively associated with Δ VA (estimate -963.08 , $p = 0.032$, $R^2 = 0.077$). A higher PD sup ($p = 0.017$, $R^2 = 0.094$), VLD sup ($p = 0.033$, $R^2 = 0.054$), and FD sup ($p = 0.043$, $R^2 = 0.069$) were positively associated with greater VA gains. In the multivariable model the full model explained 19% of the variance in Δ VA ($R^2 = 0.190$). HRF remained a strong independent predictor of limited VA improvement ($p < 0.001$, partial $R^2 = 0.104$) (**Tables 6,7**).

Discussion

This study investigated potential predictors of VA following anti-VEGF therapy based on baseline OCT and OCTA features. Despite advances in retinal imaging, many studies have not adequately acknowledged the critical prognostic role of integrated assessment of structural OCT and vascular OCTA biomarkers in diabetic macular edema (DME).^{21,42–44} Univariable models have consistently identified fluid and thickness as relevant predictors; however, their effects diminished in multivariable analysis once photoreceptor and vascular biomarkers were included supporting the view that fluid metrics alone are incomplete predictors of visual outcomes.

At baseline, several OCT-derived features were significantly associated with VA on univariable analysis, and CSFT emerged as the strongest predictor. This finding is consistent with prior observations that increased retinal thickening reflects edema severity and correlates with reduced vision in DME.^{20,42} Outer

retinal integrity markers including the EZ and ELM also showed significant associations in the univariable setting. EZ disruption ratio and ELM disruption ratio were strongly correlated with worse VA, emphasizing the critical role of photoreceptor preservation in baseline function. These results align with the recent meta-analysis by Nanji et al.⁴² which confirmed that disruption of EZ and ELM are among the most consistent OCT biomarkers linked to reduced visual function across multiple studies.

When these predictors were examined together in a multivariable model, CSFT was independently significant while the effects of EZ and ELM disruption were lost. This hierarchy suggests that at the baseline time point, macular edema burden exerts the greatest impact on visual function, while outer retina disruption contributes additional, though lesser, variance once edema is accounted for.^{16–18,20,21,42} Prior studies have demonstrated that while baseline outer retinal biomarkers are predictive, thickness remains the dominant driver of baseline VA with other structural biomarkers exerting greater influence on longer-term outcomes.^{17–20}

By 52 weeks, the strongest univariable predictors were EZ and ELM disruption, together with vascular density metrics (PD sup, VLD sup) and CSFT. This pattern aligns with past studies identifying that reduced perfusion and vessel density along with FAZ enlargement were independently associated with worse VA in DME. Similarly, DaCosta et al.,¹⁷ and Hsiao et al.,¹⁹ confirmed that OCT angiographic vessel loss correlates with VA reduction and disease severity. These associations suggest that both microvascular metrics and edema burden retain relevance in the intermediate term.^{16,18,19,21}

The multivariable model explained 28% of the variance in VA at week 52; CSFT and the PD/VLD remained independent predictors whereas EZ and ELM disruption lost significance. This highlights two key insights. First, the functional effect of photoreceptor disruption though clear in univariable analysis may be partially mediated by persistent edema and vascular compromise which dominate the variance once combined. Importantly, microvascular dropout reflected by perfusion reduction and vessel density loss exerted an independent effect on vision in line with OCTA studies linking reduced perfusion density to limited recovery.^{19,21,42–44} These results suggest a time-dependent evolution of predictive factors and reflect a transition from short-term fluid-driven changes toward longer-term perfusion constraints on vision.

Despite prior studies that demonstrate that hard exudate (likely HRF on OCT) or HRF does not affect vision outcomes,⁴⁵ in the current analysis, HRF were negatively associated with VA improvement consistent with other prior evidence that HRF represent inflammatory or lipid-laden deposits associated with chronic damage and worse treatment response.^{15,20,21,42} HRF carried the largest independent contribution in multivariable analysis, overshadowing vascular density metrics. Nonetheless, univariable associations between change in vision and perfusion/vascular density (PD, VLD, FD) suggest that preserved microvascular perfusion supports functional gains, a finding also seen in OCTA studies of DR progression.^{17,21} Thus, while HRF-rich eyes have limited recovery potential, eyes with intact vascular networks have still the chance for significant improvement. Other variables such as EZ or ELM

disruption, did not correlate significantly with change in VA, implying that once vision is already compromised by outer retinal damage further functional recovery may be less dependent on outer retina status and more influenced by vascular preservation and inflammation. This likely reflects the distinction between factors influencing baseline vision versus those that determine treatment response and recovery potential.

This study has several limitations. First, the retrospective post-hoc design introduces potential selection and confounding biases. Second, the sample size was relatively small, limiting statistical power and possibly contributing to attenuation of effects for some predictors in the multivariable analysis. Third, the manual and semi-automated grading of OCT and OCTA biomarkers may introduce some subjectivity to the analysis although certified reading center graders were used. Additionally, we focused primarily on central retinal measures, whereas peripheral microvascular changes may also contribute to functional outcomes, but were not captured.

In summary, this post-hoc analysis suggests that baseline VA was driven largely by edema burden while long-term outcomes reflected outer retinal integrity and vascular status. HRF limited visual gains and fluid metrics alone cannot fully predict functional recovery.

Abbreviations

anti-VEGF = anti-vascular endothelial growth factor; CI-DME = center-involved diabetic macular edema; CSFT = central subfield thickness; DRIL = disorganization of retinal inner layers; DVC = deep vascular complex; ΔVA = change in visual acuity (from baseline to week 52); ELM = external limiting membrane; ETDRS = Early Treatment Diabetic Retinopathy Study; EZ = ellipsoid zone; FD = fractal dimension; HRF = hyperreflective foci; OCT = optical coherence tomography; OCTA = optical coherence tomography angiography; PD = perfusion density; SRF = subretinal fluid; SVC = superficial vascular complex; VA = visual acuity; VLD = vessel length density.

Declarations

Conflicts of interest:

SriniVas Sadda: Consultant (C): Roche/Genentech, Regeneron, Allergan/Abbvie, Novartis, Amgen, Alnylam, Alkeus, Neurotech, 4DMT, Alexion, Nanoscope, Biogen, Apellis, Astellas, ONL Therapeutics, Optos, Oxurion, Pfizer, Boehringer Ingelheim, Surrozen, Arrowhead Pharma, Notal, Heidelberg Engineering, iCare, Samsung Bioepis, Eyestem, Topcon, . Recipient (R): Topcon Medical Systems Inc. Heidelberg Engineering, Nidek Incorporated, Novartis Pharma AG; Roche. Financial Support (F): Topcon, Carl Zeiss Meditec, Heidelberg Engineering, Optos Inc., Nidek, iCare/Centervue, Intalight.

Michael Ip: Consultant (C): Alimera, Allergan, Amgen, Apellis, Astellas, Boehringer Ingelheim, Clearside Biomedical, Genentech, Inc., Novartis, Regeneron Pharmaceuticals, Inc., Zeiss. Research Financial Support (F): Adverum, Apellis, Biogen, Boehringer Ingelheim, Genentech, Lineage Cell Therapeutics, Novartis, ONL Therapeutics, Regeneron Pharmaceuticals, Inc., Regenexbio, SpliceBio, 4DMT.

Giulia Corradetti: Recipient (R): Nidek, Character Bioscience, Chugai Pharmaceutical, Astellas Pharma Inc.

None of the remaining authors has any conflicts of interests.

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Tables

Tables 1 to 7 are available in the Supplementary Files section.

Figures

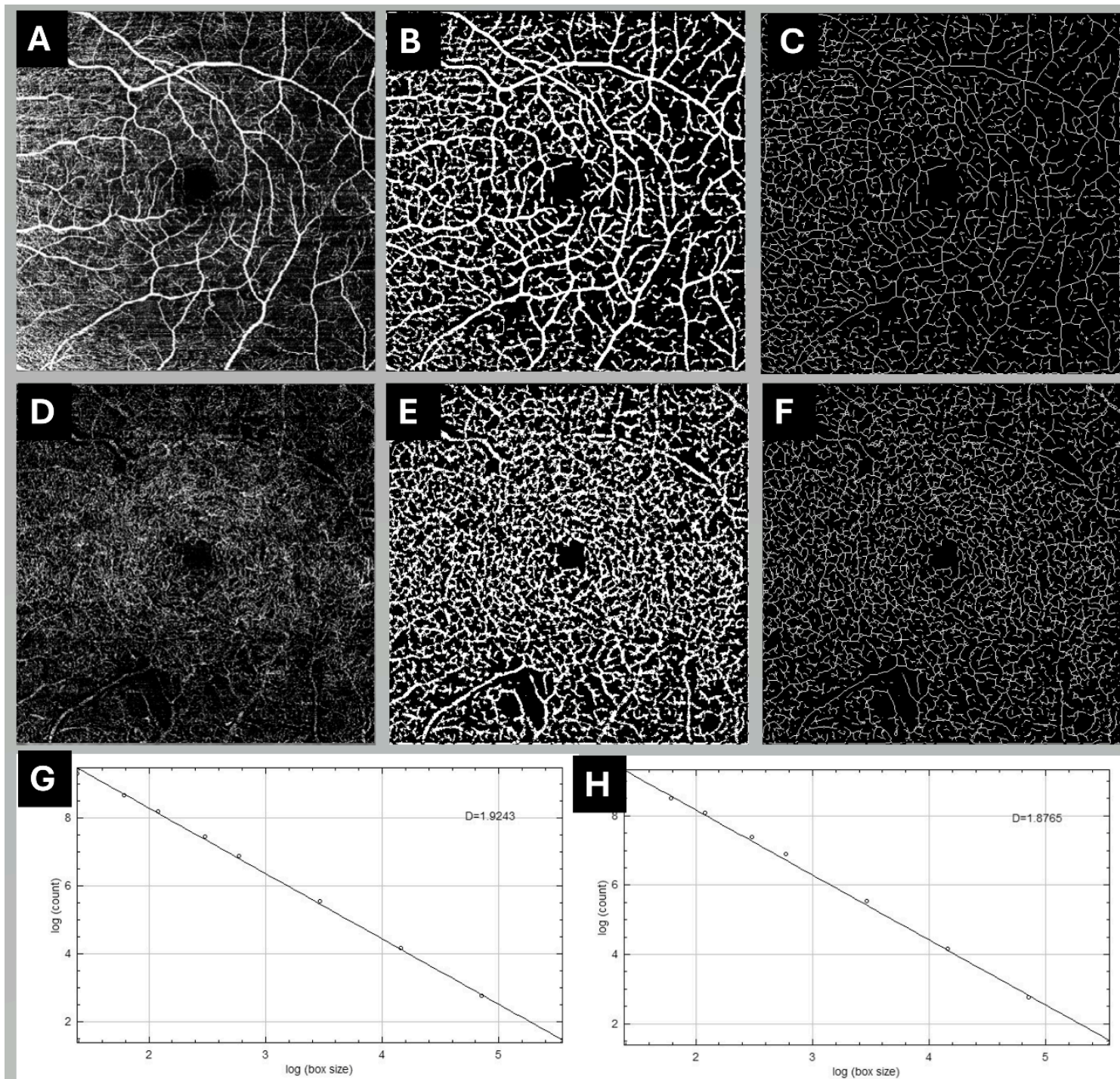


Figure 1

Quantitative analysis of Optical coherence tomography angiography workflow, (A) Spectral-domain optical coherence tomography angiography (OCTA) image segmented through the superficial vascular complex (SVC). (B) Binarized SVC to isolate perfused vasculature. (C) Skeletonized SVC image, used for vessel length density and fractal analysis. (D) OCTA image segmented through the deep vascular complex (DVC). (E) Binarized DVC image. (F) Skeletonized DVC image. (G) Fractal analysis of the SVC showing the log–log box plot used to calculate the fractal dimension (FD = 1.9243). (H) Fractal analysis of the DVC, displayed as in (G), with FD = 1.8765.

Supplementary Files

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