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# Automated Macular Fluid Volume As a Treatment Indicator for Diabetic Macular Edema

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## Abstract

**Introduction:** To assess the diagnostic accuracy of automatically quantified macular fluid volume (MFV) for treatment-required diabetic macular edema (DME). **Methods**: This retrospective cross-sectional study included eyes with DME. The commercial software on optical coherence tomography (OCT) produced the central subfield thickness (CST), and a custom deep-learning algorithm automatically segmented the fluid cysts and quantified the MFV from the volumetric scans of an OCT angiography system. Retina specialists treated patients per standard of care based on clinical and OCT findings without access to the MFV. The main outcome measures were the area under the receiver operating characteristic curve (AUROC), sensitivity, and specificity of the CST, MFV, and visual acuity (VA) for treatment indication. **Results**: Of 139 eyes, 39 (28%) were treated for DME during the study period and 101 (72%) were previously treated. The algorithm detected fluid in all eyes; however, only 54 eyes (39%) met the DRCR.net criteria for center-involved ME. The AUROC of MFV predicting a treatment decision of 0.81 was greater than that of CST (0.67) ($P = .0048$). Untreated eyes that met the optimal threshold for treatment-required DME based on MFV ($>0.031$ mm$^3$) had better VA than treated eyes ($P = .0053$). A multivariate logistic regression model showed that MFV ($P = .0008$) and VA ($P = .0061$) were significantly associated with a treatment decision, but CST was not. **Conclusions**: MFV had a higher correlation with the need for treatment for DME than CST and may be especially useful for ongoing management of DME.

## Keywords

DME, diabetic retinopathy, macular fluid volume, deep learning, 3-dimensional, AI

## Introduction

Diabetic retinopathy (DR) is the leading cause of preventable vision loss in the working-age population worldwide,[1] and diabetic macular edema (DME) is the predominant cause of vision loss.[2,3] A biomarker that has high diagnostic accuracy for DME and objectively guides treatment decisions can potentially make screening more effective and the outcomes more consistent. Advances in deep learning have made reliable automated segmentation of features from optical coherence tomography (OCT) possible.[4–8] We recently reported a deep-learning algorithm that quantifies the macular fluid volume (MFV) by automatically segmenting fluid cysts from dense B-scans.[6] This approach could diagnose DME more accurately than the central subfield thickness (CST) compared with the ground truth of human graders.[9] However, it remains unclear whether MFV can better identify eyes that would require treatment.

When making a treatment decision for DME, clinicians consider a number of factors, including the extent and the location of the edema as well as the visual acuity (VA).[10] The Diabetic Retinopathy Clinical Research (DRCR) Retina Network Protocol V reported that in eyes with center-involved DME and a VA of 20/25 or better, there was no difference in VA when the eyes were treated immediately with aflibercept vs when treatment was deferred until the VA decreased to 20/32.[11] Because MFV is more sensitive for DME, it is possible that a screening approach that relies on MFV would identify more eyes with DME that does not need to be treated, unnecessarily increasing the burden on the healthcare system.

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To address this concern, we performed a cross-sectional study to evaluate whether MFV can be used to distinguish eyes that require treatment for DME. We analyzed the relationship between MFV, CST, and VA on the clinician's treatment decision for DME in real clinical practice.

## Methods

This cross-sectional retrospective study cohort comprised 2 prospective OCT/OCT angiography (OCTA) studies (NIH R01 EY027833) performed at Casey Eye Institute, Oregon Health Science University. The details of the studies have been published.[9,12–15] The study adhered to the tenets of the Declaration of Helsinki and complied with the US Health Insurance Portability and Accountability Act of 1996. The Institutional Review Board of Oregon Health Science University approved the study. All participants provided written informed consent to participate in the OCT/OCTA studies. All participants were enrolled from February 17, 2015, to December 23, 2019, and data analysis for the current study was performed from October 2020 to January 2022.

All participants were recruited in the retina service at Casey Eye Institute. The study included diabetic eyes with intraretinal or subretinal fluid detected by a deep-learning algorithm from the 3.0 mm × 3.0 mm OCT volume. The study excluded pregnant or lactating women, those unable to consent or cooperate with OCT or OCTA scans, or those with significant nondiabetic ocular diseases such as age-related macular degeneration. Also excluded were eyes with a history of intraocular surgery except cataract surgery. Eyes with recent intravitreal injections were included. Only 1 eye of each participant was included in the study.

In all cases, the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol was used to assess VA.[16] Intraocular pressure measurement, slitlamp biomicroscopy, and indirect binocular ophthalmoscopy were also performed.

Imaging included standard 7-field ETDRS color fundus photography, 6.0 mm × 6.0 mm macular structural OCT raster scans (19 horizontal B-scans; automatic real-time tracking function set at a mean of 9 frames) using the Spectralis system (Heidelberg) and 3.0 mm × 3.0 mm macular OCTA scan pattern using the Avanti system (Optovue). A single OCTA scan generates both structural volumetric OCT and OCTA. In this study, only the structural OCT volume (304 × 304 A-lines) was used for retinal fluid detection. A retina specialist (T.S.H.) assessed the severity of DR based on standard 7-field ETDRS color fundus photographs using the ETDRS severity scale. The retina specialists made treatment decisions according to the standard of care based on the clinical and OCT raster scans without access to the MFV generated from the OCTA scans.[10]

The DRCR.net study definition of center-involved edema (CST ≥ 320 mm in men; CST ≥ 305 mm in women) was used.[17] The software embedded on the OCT machine calculated the CST, defined as the mean thickness within the 1.0 mm circle centered on the fovea (Heyex, version 6.8.3, Heidelberg). Expert graders reviewed and corrected the segmentation of the internal limiting membrane and retinal pigment epithelium (RPE)–Bruch membrane for accuracy. An algorithm based on deep learning automatically quantified the MFV, including intraretinal and subretinal fluid, from the 3.0 mm × 3.0 mm OCTA volume.[6,18] Based on the location of the fluid, the COOL ART OCTA signal-processing tool (developed at the Center for Ophthalmic Optics & Lasers Lab, Casey Eye Institute) was used to further divide the fluid into (1) the inner nuclear layer (INL) fluid, within the borders of the INL, (2) the outer retinal fluid, bounded by the outer border of the INL to the ellipsoid zone, and (3) the subretinal fluid, located between the ellipsoid zone and the RPE.[19,20] This segmentation of the retinal layers was manually confirmed and corrected. The details of this algorithm have been described.[19,20]

Descriptive statistics included the mean ± SD, range, and percentages where appropriate. The area under the receiver operating characteristic curve (AUROC) for predicting the treatment decision was calculated for the CST, MFV, and VA and compared using the method of DeLong et al.[21] Univariate and multivariate logistic regression analyses assessed the relationship between the treatment decision and baseline parameters. In the multivariate logistic regression model, a nonstandardized odds ratio (OR) and standardized coefficient were computed using the Agresti[22] method. The sensitivities were compared using the McNemar test. All analyses were performed using JMP software (version 13.1.0, SAS Institute) and R statistical language (R Foundation). All $P$ values were from 2-sided tests, and results were deemed statistically significant at $P < .05$.

## Results

The study enrolled 1 eye each of 139 diabetic patients with any fluid detected by the algorithm in the 3.0 mm × 3.0 mm OCTA scan area. Table 1 shows the baseline and clinical characteristics of the patients. The most common DR stage was proliferative DR (PDR) (36.7%) followed by severe nonproliferative PDR (25.9%). The majority of eyes had no treatment in the 4 months before the baseline visit (71%) and had a history of hypertension (77.0%).

The algorithm detected fluid in all 139 eyes; however, only 54 eyes (39%) met the DRCR.net criteria for center-involved ME. The mean MFV was 0.062 ± 0.14 $mm^3$ (95% CI, 0.039 to 0.085). Thirty-nine eyes (29%) had treatment for DME at the baseline visit, including intravitreal antivascular endothelial growth factor (anti-VEGF) injections in 36 eyes (92%) and intravitreal steroid injections in 3 eyes (8%).

The AUROC of MFV for detecting eyes that had treatment was 0.81 (95% CI, 0.73 to 0.90) (Figure 1 and Table 2). The corresponding Youden index $J$ statistic was 0.58 (95% CI, 0.21 to 0.84), and the optimal threshold was 0.031 $mm^3$ (95% CI, 0.010 to 0.070). The AUROC of MFV for detecting treated eyes was larger than that of CST (0.67; 95% CI, 0.56 to 0.78; $P = .0048$) but not significantly larger than that of VA

**Table 1.** Demographic and Clinical Characteristics of Study Participants.

| Parameter | Value |
|---|---|
| Age (y) | |
| Mean ± SD | 59.9 ± 12.1 |
| Range | 26, 80 |
| Sex (n) | |
| Male | 74 |
| Female | 65 |
| Most recent $Hb_{A1c}$ (%) | |
| Mean ± SD | 7.7 ± 1.6 |
| Range | 5.2, 8.8 |
| Systolic blood pressure (mm Hg) | |
| Mean ± SD | 132 ± 21 |
| Range | 84, 195 |
| Diastolic blood pressure (mm Hg) | |
| Mean ± SD | 74 ± 14 |
| Range | 43, 110 |
| History of hypertension, n (%) | 107 (77.0) |
| DR stage, n (%) | |
| DM without DR | 1 (0.7) |
| Mild NPDR | 25 (18.0) |
| Moderate NPDR | 26 (18.7) |
| Severe NPDR | 36 (25.9) |
| PDR, n | 51 (36.7) |
| Axial length (mm) | |
| Mean ± SD | 23.6 ± 1.0 |
| Range | 21.2, 26.3 |
| Mean BCVA, ETDRS letters | |
| Mean ± SD | 75.9 ± 8.7 |
| Range | 40, 93 |
| Mean CST (μm) | |
| Mean ± SD | 321 ± 82 |
| Range | 180, 686 |
| Treatment naïve eyes, n (%) | 38 (27) |
| No treatment in 4 months before baseline visit, n (%) | 99 (71) |
| History of focal photocoagulation, n (%) | 33 (24) |

Abbreviations: BCVA, best-corrected visual acuity; CST, central subfield thickness; DM, diabetes mellitus; DR, diabetic retinopathy; ETDRS, Early Treatment Diabetic Retinopathy Study; $Hb_{A1c}$, hemoglobin A1c; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.

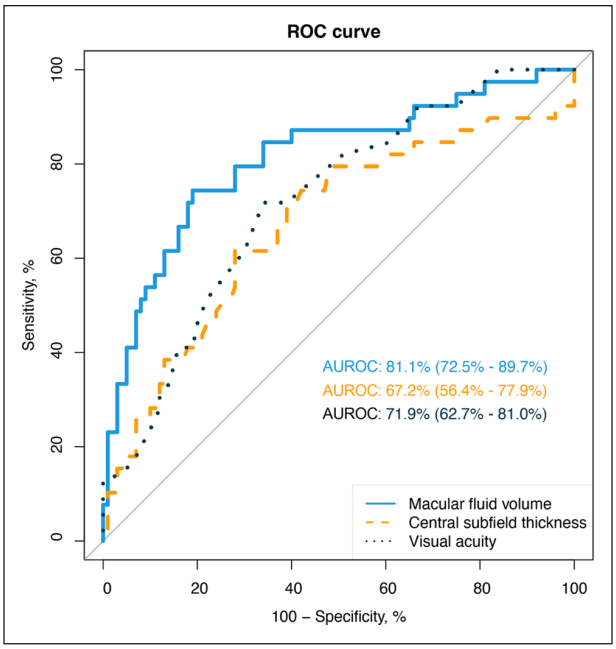


**Figure 1.** The area under the receiver operating characteristic curve (AUROC) for predicting treatment decision. The AUROC of macular fluid volume for a treatment indication was larger than the AUROC of central subfield thickness (0.67; 95% CI, 0.56 to 0.78; $P = .0048$) but not significantly larger than the AUROC of visual acuity (0.72; 95% CI, 0.63 to 0.81; $P = .14$).

(0.72; 95% CI, 0.63 to 0.81; $P = .14$). When eyes without treatment in the preceding 4 months (n = 99) and eyes without previous focal photocoagulation (n = 106) were separately analyzed, the AUROCs of MFV, CST, and VA were similar (Table 3).

The multiple logistic regression model including MFV, VA, and CST as explanatory variables showed that MFV (OR for every 0.01 $mm^3$ MFV increase, 1.15 [95% CI, 1.01 to 1.26]; standardized coefficient, 1.88 [95% CI, 0.92 to 3.03]; $P = .0008$) and VA (OR for every 1 letter score increase, 0.92 [95% CI, 0.87 to 0.97]; standardized coefficient, −0.72 [95% CI, −1.25 to −0.22]; $P = .0061$) were statistically significant factors. The AUROC of the multivariate logistic regression model combining MFV and VA was 0.82 (95% CI, 0.75 to 0.90).

When sensitivity was set at 90%, MFV could predict treatment with a specificity of 34.0% (95% CI, 25.0% to 45.0%; threshold, 0.0018 $mm^3$), which was higher than that of CST (18.0% [95% CI, 11.0% to 26.0%]; threshold, 260.5 mm) ($P < .0001$). When the specificity was set at 80%, MFV could predict treatment with a sensitivity of 74.4% (95% CI, 61.5% to 87.2%; threshold, 0.031 $mm^3$), higher than that of CST (41.0% [95% CI, 25.6% to 56.4%]; threshold, 340.5 mm) ($P = .0007$).

Physicians did not treat 20 eyes that met the MFV threshold set for 80% specificity (>0.031 $mm^3$). Compared with eyes with MFV of 0.031 $mm^3$ or more that were treated (n = 29), untreated eyes had better VA (mean 77.9 ± 7.3 letters vs 70.3 ± 10.8 letters; $P = .0053$, $t$ test) but similar CST (mean thickness, 363 ± 97 mm vs 381 ± 105 mm; $P = .56$).

Using the DRCR.net study definition of center-involved edema with the CST, the sensitivity for a treatment decision by the physician was 61.5% and the specificity was 70.0% (Table 4), meaning 15 eyes (39%) that were treated did not meet these criteria. Compared with treated eyes that met the criteria (n = 24), these eyes had a higher proportion of previous macular laser treatment (7 of 15 [46.7%] vs 2 of 24 [8.3%]; $P = .015$), a thinner CST (mean 268 ± 47 mm vs 409 ± 93 mm; $P < .0001$), and a smaller MFV (mean 0.051 ± 0.048 $mm^3$ vs 0.22 ± 0.26 $mm^3$; $P = .0047$). For the 54 eyes that had center-involved edema by the DRCR criteria, the treated eyes (n = 24) had a greater MFV (mean 0.22 ± 0.26 $mm^3$ vs 0.040 ± 0 .044 $mm^3$; $P < .0001$) and a trend toward a worse VA (mean

**Table 2.** AUROC for Treatment Indications.

| Parameter | AUROC (95% CI) | Threshold[a] (95% CI) | Sensitivity[a] (95% CI) | Specificity[a] (95% CI) |
|---|---|---|---|---|
| MFV ($mm^3$) | 81.1 (72.5-89.7) | 0.031 (0.010-0.070) | 0.77 (0.61-0.92) | 0.81 (0.63-0.92) |
| BCVA (ETDRS letter score) | 71.9 (62.7-81.0) | 78.8 (71.5-82.5) | 0.74 (0.51-0.95) | 0.67 (0.47-0.89) |
| CST (mm) | 67.2 (56.4-77.9) | 307.5 (295-371.5) | 0.72 (0.41-0.90) | 0.67 (0.47-0) |

Abbreviations: AUROC, area under the receiver operating characteristic curve; BCVA, best-corrected visual acuity; CST, central subfield thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; MFV, macular fluid volume.
[a]Threshold, sensitivity, and specificity were computed with the optimal threshold based on the Youden *J* statistic.

**Table 3.** Subgroup Analysis of AUROC for Treatment Indications.

| | AUROC (95% CI) | |
|---|---|---|
| Parameter | Eyes Without Treatment in Preceding 4 Mo From Baseline Visit (n = 99) | Eyes Without History of Focal Photocoagulation (n = 106) |
| MFV ($mm^3$) | 0.78 (0.59-0.97) | 0.86 (0.78-0.95) |
| BCVA (ETDRS letter score) | 0.69 (0.53-0.85) | 0.69 (0.58-0.80) |
| CST (mm) | 0.66 (0.44-0.88) | 0.71 (0.59-0.83) |

Abbreviations: AUROC, area under the receiver operating characteristic curve; BCVA, best-corrected visual acuity; CST, central subfield thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; MFV, macular fluid volume.

**Table 4.** Treatment Indication by Physician vs MFV, CST, or DRCR.net Criteria.

| | Treatment Indication by Physicians (n) | | |
|---|---|---|---|
| Grading | Treated Eyes (n = 39) | Untreated Eyes (n = 100) | Total |
| Treatment indication by MFV (threshold, 0.0018 $mm^3$) | | | |
| Yes | 35 | 66 | 101 |
| No | 4 | 34 | 38 |
| Treatment indication by CST (threshold, 260.5 μm) | | | |
| Yes | 35 | 83 | 118 |
| No | 4 | 17 | 21 |
| Treatment indication by DRCR.net criteria[a] | | | |
| Yes | 24 | 30 | 54 |
| No | 15 | 70 | 85 |

Abbreviations: CST, central subfield thickness; DRCR, Diabetic Retinopathy Clinical Research; MFV, macular fluid volume.
[a]CST ≥320 μm in men; CST ≥305 μm in women.

72.0 ± 9.6 letters vs 76.5 ± 7.1 letters; $P = .060$) than the untreated eyes (n = 30).

## Conclusions

Our study found that MFV based on the deep-learning algorithm is better than CST not only for the diagnosis of DME but also for detecting the need for treatment for DME in the ongoing treatment cohort. The MFV, by measuring more specific features for ME compared with CST, may be a more useful biomarker.[6,9,23] In our previous study,[9] we found that the MFV can detect center-involved ME that clinicians diagnosed with higher accuracy than CST. Here, we showed that a higher MFV is also more closely associated with a physician's treatment decision for DME than CST.

The present study simulates how MFV can be applied in real clinical settings. Because MFV has a high diagnostic accuracy for detecting DME,[9] a potential concern was that MFV may identify more eyes with DME that does not need to be treated. The current results show that MFV is useful for detecting treatment-required DME compared with CST, suggesting MFV is a meaningful quantifiable biomarker.

All modern clinical trials evaluating the efficacy of treatment for DME have focused on the OCT-derived CST and VA.[24–26] CST has provided an objective measure of retinal thickening that previous trials lacked.[27] However, CST has a normal population variation,[17] meaning some eyes without ME will have abnormal values and some eyes with DME will have values within normal limits. In contrast,

only eyes with ME should have detected fluid volume, which means MFV should be much more specific for DME than CST. Although we have demonstrated the accuracy of the network at the voxel level in previous work,[6] a larger study may be needed to show its advantage over CST at the population level.

Retinal atrophy from previous photocoagulation or ischemia can reduce the CST measurement to a normal range in eyes with DME.[28] However, CST remains the gold standard for following the treatment response in DME. There is a moderate correlation between the change in VA and change in CST after anti-VEGF therapy.[29] It has been incorporated into treatment protocols used by the DRCR.net studies. Theoretically, MFV could also serve the purpose of following treatment response while more accurately identifying eyes with DME, potentially replacing CST. However, although it may be true that MFV is less prone to confounding related to atrophy or epiretinal membranes than CST, we do not know whether there are significant DME-related changes in the tissue that MFV might not detect. It is possible that interstitial edema can change the volume of retinal tissue without manifesting as detectable fluid cysts,[23] which might be significant in the disease process. The only certain way to demonstrate the equivalence or superiority of the biomarker is with a prospective trial that examines meaningful clinical outcomes.

It is well established that center-involved DME by DRCR CST criteria is not a sufficient indication for treatment because eyes with good vision can be observed.[11,30] In this study, physicians chose to observe eyes with MFV greater than the threshold with good vision. Although the multivariate analysis showed that controlling for VA MFV was still a significant factor in detecting the treatment, VA remains an essential consideration in making treatment decisions.

A key limitation of our study is that the study population was not a treatment-naïve group and may have been in the middle of a treatment course when the baseline image took place. Previous treatment and its response may have been an essential factor in a treatment decision, and the current study design does not allow us to assess these factors. In addition, retina specialists treated the current patients. (Almost 80% of the entire cohort was treated by 3 physicians [C.J.F, S.T.B, T.S.H.].) Also, the study did not prescribe a treatment protocol but observed a real-world situation in which physicians with non-uniform preferences made decisions with patient input. A potential variation in physician practice patterns as well as patient preference could have influenced the number of injections. Finally, DRCR Retinal Network study Protocol V[11] was reported in May 2019, and its results may have had an impact on the treatment of center-involved DME with good VA given that our cohort spanned time periods (February 2015 to December 2019) before and after the publication of this study. To validate the clinical value of MFV, further studies including large number of datasets that span multiple centers are essential.

In conclusion, MFV is a biomarker that is more specific to the disease process in DME and may better detect treatment-required DME than CST in eyes with ongoing DME treatment. Modern OCT/OCTA devices enable a high-quality, dense macular scan that allows for reliable and accurate quantification of retinal fluid without requiring uncomfortable extended scans. Because it is better at detecting real-world physician decisions to treat in the previously treated cohort, it could be a meaningful biomarker in a screening setting.

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## Ethical Approval

The Institutional Review Board of Oregon Health Science University approved the study.

## Statement of Informed Consent

All participants provided a written informed consent to participate in the OCT/OCTA studies.

## Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Oregon Health & Science University (OHSU) and Drs. Jia and Huang have a significant financial interest in Optovue Inc, a company that may have a commercial interest in the results of this research and technology. These potential conflicts of interest have been reviewed and managed by OHSU. Dr. Tsuboi has a financial interest unrelated to the current manuscript from Alcon Japan Ltd, Abbott Medical Optics, Santen Co, Ltd, Novartis Pharma KK, and Bayer. No other disclosures were reported.

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## Reference

1. Cheung N, Mitchell P, Wong TY. Diabetic retinopathy. *Lancet*. 2010;376(9735):124-136. doi:10.1016/S0140-6736(09)62124-3
2. Yau JW, Rogers SL, Kawasaki R, et al. Global prevalence and major risk factors of diabetic retinopathy. *Diabetes Care*. 2012;35(3):556-564. doi:10.2337/dc11-1909
3. Tan GS, Cheung N, Simó R, Cheung GC, Wong TY. Diabetic macular oedema. *Lancet Diabetes Endocrinol*. 2017;5(2):143-155. doi:10.1016/S2213-8587(16)30052-3

4. Schmidt-Erfurth U, Sadeghipour A, Gerendas BS, Waldstein SM, Bogunović H. Artificial intelligence in retina. *Prog Retin Eye Res*. 2018;67:1-29. doi:10.1016/j.preteyeres.2018.07.004
5. Schlegl T, Waldstein SM, Bogunovic H, et al. Fully automated detection and quantification of macular fluid in OCT using deep learning. *Ophthalmology*. 2018;125(4):549-558. doi:10.1016/j.ophtha.2017.10.031
6. Guo Y, Hormel TT, Xiong H, Wang J, Hwang TS, Jia Y. Automated segmentation of retinal fluid volumes from structural and angiographic optical coherence tomography using deep learning. *Transl Vis Sci Technol*. 2020;9(2):54. doi:10.1167/tvst.9.2.54
7. Schmidt-Erfurth U, Vogl WD, Jampol LM, Bogunović H. Application of automated quantification of fluid volumes to anti-VEGF therapy of neovascular age-related macular degeneration. *Ophthalmology*. 2020;127(9):1211-1219. doi:10.1016/j.ophtha.2020.03.010
8. Wilson M, Chopra R, Wilson MZ, et al. Validation and clinical applicability of whole-volume automated segmentation of optical coherence tomography in retinal disease using deep learning. *JAMA Ophthalmol*. 2021;139(9):964-973. doi:10.1001/jamaophthalmol.2021.2273
9. You QS, Tsuboi K, Guo Y, et al. Comparison of central macular fluid volume with central subfield thickness in patients with diabetic macular edema using optical coherence tomography angiography. *JAMA Ophthalmol*. 2021;139(7):734-741. doi:10.1001/jamaophthalmol.2021.1275
10. Flaxel CJ, Adelman RA, Bailey ST, et al. Diabetic retinopathy preferred practice pattern® [published correction appears in Ophthalmology. 2020 Sep;127(9):1279]. *Ophthalmology*. 2020;127(1):P66-P145. doi:10.1016/j.ophtha.2019.09.025
11. Baker CW, Glassman AR, Beaulieu WT, et al. Effect of initial management with aflibercept vs. laser photocoagulation vs. observation on vision loss among patients with diabetic macular edema involving the center of the macula and good visual acuity: a randomized clinical trial. *JAMA*. 2019;321(19):1880-1894. doi:10.1001/jama.2019.5790
12. Hwang TS, Jia Y, Gao SS, et al. Optical coherence tomography angiography features of diabetic retinopathy. *Retina*. 2015;35(11):2371-2376. doi:10.1097/IAE.0000000000000716
13. Hwang TS, Gao SS, Liu L, et al. Automated quantification of capillary nonperfusion using optical coherence tomography angiography in diabetic retinopathy. *JAMA Ophthalmol*. 2016;134(4):367-373. doi:10.1001/jamaophthalmol.2015.5658
14. Hwang TS, Hagag AM, Wang J, et al. Automated quantification of nonperfusion areas in 3 vascular plexuses with optical coherence tomography angiography in eyes of patients with diabetes. *JAMA Ophthalmol*. 2018;136(8):929-936. doi:10.1001/jamaophthalmol.2018.2257
15. You QS, Guo Y, Wang J, et al. Detection of clinically unsuspected retinal neovascularization with wide-field optical coherence tomography angiography. *Retina*. 2020;40(5):891-897. doi:10.1097/IAE.0000000000002487
16. Early Treatment Diabetic Retinopathy Study design and baseline patient characteristics. ETDRS report number 7. *Ophthalmology*. 1991;98(5 suppl):741-756. doi:10.1016/s0161-6420(13)38009-9
17. Chalam KV, Bressler SB, Edwards AR, et al. Retinal thickness in people with diabetes and minimal or no diabetic retinopathy: Heidelberg Spectralis optical coherence tomography. *Invest Ophthalmol Vis Sci*. 2012;53(13):8154-8161. doi:10.1167/iovs.12-10290
18. Wang J, Zhang M, Pechauer AD, et al. Automated volumetric segmentation of retinal fluid on optical coherence tomography. *Biomed Opt Express*. 2016;7(4):1577-1589. doi:10.1364/BOE.7.001577
19. Zhang M, Wang J, Pechauer AD, et al. Advanced image processing for optical coherence tomographic angiography of macular diseases. *Biomed Opt Express*. 2015;6(12):4661-4675. doi:10.1364/BOE.6.004661
20. Guo Y, Camino A, Zhang M, et al. Automated segmentation of retinal layer boundaries and capillary plexuses in wide-field optical coherence tomographic angiography. *Biomed Opt Express*. 2018;9(9):4429-4442. doi:10.1364/BOE.9.004429
21. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics*. 1988;44(3):837-845.
22. Agresti A. *An Introduction to Categorical Data Analysis*. 2nd ed. John Wiley & Sons; 2007.
23. Tsuboi K, You QS, Guo Y, et al. Association between fluid volume in inner nuclear layer and visual acuity in diabetic macular edema. *Am J Ophthalmol*. 2022;237:164-172. doi:10.1016/j.ajo.2021.12.012
24. Nguyen QD, Brown DM, Marcus DM, et al. Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. *Ophthalmology*. 2012;119(4):789-801. doi:10.1016/j.ophtha.2011.12.039
25. Mitchell P, Bandello F, Schmidt-Erfurth U, et al. The RESTORE study: ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema. *Ophthalmology*. 2011;118(4):615-625. doi:10.1016/j.ophtha.2011.01.031
26. Heier JS, Korobelnik JF, Brown DM, et al. Intravitreal aflibercept for diabetic macular edema: 148-week results from the VISTA and VIVID studies. *Ophthalmology*. 2016;123(11):2376-2385. doi:10.1016/j.ophtha.2016.07.032
27. Browning DJ, Glassman AR, Aiello LP, et al. Optical coherence tomography measurements and analysis methods in optical coherence tomography studies of diabetic macular edema. *Ophthalmology*. 2008;115(8):1366-1371.e1. doi:10.1016/j.ophtha.2007.12.004
28. Rutledge BK, Wallow IH, Poulsen GL. Sub-pigment epithelial membranes after photocoagulation for diabetic macular edema. *Arch Ophthalmol*. 1993;111(5):608-613. doi:10.1001/archopht.1993.01090050042025
29. Bressler NM, Odia I, Maguire M, et al. Association between change in visual acuity and change in central subfield thickness during treatment of diabetic macular edema in participants randomized to aflibercept, bevacizumab, or ranibizumab: a post hoc analysis of the protocol T randomized clinical trial. *JAMA Ophthalmol*. 2019;137(9):977-985. doi:10.1001/jamaophthalmol.2019.1963
30. Glassman AR, Baker CW, Beaulieu WT, et al. Assessment of the DRCR retina network approach to management with initial observation for eyes with center-involved diabetic macular edema and good visual acuity: a secondary analysis of a randomized clinical trial. *JAMA Ophthalmol*. 2020;138(4):341-349. doi:10.1001/jamaophthalmol.2019.6035