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Association of Macular Vessel Density and Ganglion Cell Complex Thickness with Central Visual Field Progression in Glaucoma

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Abstract

Background/Aims: To evaluate the association of macular vessel density (VD) and ganglion cell complex (GCC) thickness with 10–2 central visual field (CVF) progression in glaucoma.

Methods: In this retrospective cohort study, glaucoma patients from Diagnostic Innovation in Glaucoma Study with ≥ five 10–2 visual field (VF) tests and 3-year follow-up before optical coherence tomography (OCT) and OCT angiography (OCTA) imaging were included. Whole-image GCC thickness (wiGCC) and superficial VD (wiVD) were obtained from 6*6 macula scans. The association of wiVD and wiGCC with past rate of 10–2 VF mean deviation worsening, and with past CVF progression (defined using clustered linear regression criteria) was evaluated using linear mixed models after adjusting for confounders.

Results: From 238 eyes (141 patients), 25 eyes (11%) of 16 patients were CVF progressors. In the multivariable analysis of the association between OCT/OCTA parameters and past rate of 10–2 CVF worsening, lower wiVD (β = −0.04 [−0.05, −0.02]; P<0.001; R^2=0.32) and wiGCC (β = −0.01 [−0.01, 0.00]; P=0.004; R^2=0.21) were significantly associated with faster CVF worsening. For the association between OCT/OCTA parameters and past CVF progression, the multivariable analysis showed a lower wiVD was significantly associated with increased odds of past CVF progression (OR = 1.23 [1.06, 1.44] per 1% lower; P=0.008), while wiGCC did not show correlation.

Conclusions: Lower macular VD and GCC were associated with faster worsening of CVF, and lower macular VD was associated with increased odds of CVF progression. Assessment of macular OCT and OCTA may help detect glaucoma eyes with CVF progression.

Keywords

glaucoma; vessel density; central visual field; OCTA. 10–2 visual field

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INTRODUCTION

Characterized by worsening visual field (VF) due to underlying retinal ganglion cell loss, glaucoma is a leading cause of vision impairment that has a major impact on the life of those affected.[1] The etiology of glaucoma is considered multifactorial, and it has been suggested that an alteration in the ocular microcirculation may be important.[1 2] With the recent advent of optical coherence tomography angiography (OCTA), more evidence supporting the vascular theory in glaucoma has accumulated,[2] and various associations between retinal vessel density (VD) and other functional and structural parameters have been observed.[3–6]

It is increasingly recognized that central visual field (CVF) loss can occur early in glaucoma.[7] Moreover, it is also has been reported that a defect in the CVF can have a severe impact on the patient's quality of life (QoL) and daily function.[8–11] In a prior study, a progressive decline in inferior CVF sensitivity was shown to have the strongest effect on the longitudinal QoL decline in glaucoma.[9] Thus, the early identification and timely management of patients with CVF progression is critical. However, it can be difficult for physicians to identify patients with progressive CVF loss at the time of first examination.

Some previous cross-sectional studies have found a structural-functional correlation between OCTA-measured macular VD and CVF.[12 13] Specifically, lower macular VD was associated with higher prevalence of 10–2 CVF defects. A similar cross-sectional association with 10–2 CVF has also been reported for optical coherence tomography (OCT)-measured macular thickness parameters.[14–16] Notably, prior studies have shown that lower macular VD is associated with longitudinal global 24–2 VF progression.[17 18] However, the 10–2 CVF is presumedly more relevant to QoL, and its relationship to macular VD in a longitudinal study has not been previously reported. This information would inform on whether macular VD helps identify patients at greater risk of CVF progression, who are more likely to have impaired vision-related QoL.

The objective of the current study is to evaluate if macular VD and ganglion cell complex (GCC) thickness is associated with past 10–2 CVF progression.

METHODS

The current study was approved by the University of California San Diego Human Research Protection Program (NCT00221897) and adhered to the tenets of the Declaration of Helsinki and the Health Insurance Portability and Accountability Act. Written informed consent was obtained from all participants.

Participants from the Diagnostic Innovations in Glaucoma Study (DIGS, details described previously[19 20]) meeting the inclusion criteria were included in this retrospective, observational cohort study. Briefly, all DIGS participants underwent annual comprehensive ophthalmic examination in both eyes with slit-lamp biomicroscopy, best-corrected visual acuity (BCVA), dilated fundus examination, and stereoscopic optic disc photography, and semi-annual examination of VF testing (24–2 VF and 10–2 VF), intraocular pressure (IOP) measurement with Goldmann applanation tonometry, and OCTA/OCT imaging.

Gonioscopy and ultrasound pachymetry were performed at the first visit. Other demographic information, including age, race, systemic medical history, blood pressure, and medication use, was also collected.

The overall inclusion criteria for the current study were: (1) age >18 years, (2) a diagnosis of glaucoma suspect or primary open-angle glaucoma (POAG) (3) BCVA of 20/40 or better at study entry, (4) refraction within ±5.0 diopters spherical and within ±3.0-diopters cylinder at study entry, (5) at least five 10–2 VF tests with a minimum of 3-years of follow-up before OCT/OCTA imaging, (6) a macular OCT/OCTA scan acquired within 6 months of the last VF test. Exclusion criteria were: (1) history of ocular trauma, (2) coexisting retinal pathologies, (3) non-glaucomatous optic neuropathy, (4) axial length >27 mm, and (5) uveitis. Participants were also excluded if they have been diagnosed with Parkinson's disease, Alzheimer's disease, dementia, or a history of stroke.

POAG was defined as eyes showing repeatable (on at least 2 consecutive tests) and reliable abnormal VF results (fixation losses and false negatives ≤ 33% and false positives ≤ 33%) using the 24–2 Swedish Interactive Thresholding Algorithm with a pattern standard deviation (PSD) outside 95% normal limits or a glaucoma hemifield test result outside the 99% normal limit. Glaucoma suspect was defined as having elevated IOP (≥22 mm Hg) or a suspicious-appearing optic disc (optic disc with observable neuroretinal rim narrowing or notching, excavation, or a localized or diffuse retinal nerve fiber layer [RNFL] defect suggestive of glaucoma based on standard review of stereophotographs) without a repeatable glaucomatous VF damage. Glaucoma severity was classified as early if the 24–2 VF mean deviation (MD) was greater than −6 dB, moderate if worse than −6 dB but better than −12 dB, and advanced if worse than −12 dB.

Visual Field Testing and Central Visual Field Progression

24–2 and 10–2 VF tests were performed using Swedish Interactive Threshold Algorithm standard 24–2 threshold test (Humphrey Field Analyzer 750 II-I, Carl Zeiss Meditec, Inc.). The quality of VF tests was reviewed by the Visual Field Assessment Center staff at the University of California, San Diego, with only reliable test results included. VF results were excluded if the following artifacts were present: (1) evidence of rim artifacts (non-repeatable loss around the peripheral edge of the VF) and eyelid artifacts (non-repeatable loss in the most superior VF locations), (2) inattention (elevated false negatives and/or a generally depressed or patchy field) or fatigue (defect in a "cloverleaf" pattern, normal in the center and more defective towards the edges) effects, (3) VF damage caused by diseases other than glaucoma.

In this study, the rate of CVF worsening was defined as the slope of 10–2 VF mean deviation (MD) over time, and CVF progression was defined using the clustered pointwise linear regression (PLR) criteria described in prior work.[21–23] The definition of 10–2 VF zones were based on Hood et al.[24] (Figure 1) The determination of CVF progression was based on all available 10–2 VF tests before and including the last results obtained within 6 months of OCT/OCTA examination. Briefly, a 10–2 or 24–2 VF test point was defined as worsening if there was a significantly negative slope of ≦ −1 dB per year with a significance level of $p < 0.01$, and a 10–2 CVF progression was defined as having ≥3 VF test points located in

the same latent class analysis-derived 10–2 VF zone progressing faster than −1.0 dB per year with a significance level of p< 0.01.[21 22 24] Eyes were categorized into CVF progressors and non-progressors based on the presence of 10–2 CVF progression.

Optical Coherence Tomography Angiography and Spectral-Domain Optical Coherence Tomography

Non-HD 6mm × 6mm (304-A scans in each B-scan and 304-B scans acquired) macula OCT/OCTA scans were acquired for all patients using the Avanti Angiovue system (Optovue, Inc. Fremont, CA, software version 2018.1.1.63).[25] The OCT/OCTA images were acquired simultaneously, and the thickness and VD analysis was performed on the same scan slab. The superficial VD was calculated as the percentage of measured area occupied by flowing blood vessels. The GCC thickness, consisting of the ganglion cell layer, internal plexiform layer, and RNFL, was measured from the macular cube image acquired from the OCTA scan. In the current study, superficial whole-image VD (wiVD) and whole-image GCC (wiGCC) thickness were calculated from the entire macula scan.

The quality of all OCT/OCTA images was reviewed by trained graders according to the University of California, San Diego, Imaging Data Evaluation and Analysis Reading Center standard protocol. If any of the following was present, an image was excluded based on poor quality: (1) low scan quality <4, (2) poor clarity, (3) image cropping or local weak signal, (4) residual motion artifacts visible as irregular vessel pattern on the en-face angiogram, (5) off-centered fovea, and (6) severe segmentation errors that was uncorrectable.

Statistical analysis

Continuous and categorical data are presented as mean (95% confidence interval [CI]) and counts (%). Eye characteristics were compared between CVF progressors and non-progressors using linear mixed-effects models, which accounted for the within-participant variability. Univariable and multivariable mixed models were used to evaluate the association of macular VD and GCC with the rate of past 10–2 CVF worsening, and univariable and multivariable logistic regression was used to evaluate the association with past CVF progression. After ruling out the possibility of a considerable multicollinearity by calculating the variance inflation factor,[26 27] age, baseline 10–2 VF MD, last-visit glaucoma severity, IOP, signal strength index (SSI), and any other variables that showed a P value < 0.1 in the univariable analysis were included in the multivariable model. Statistical analyses were performed using Stata version 16.0 (StataCorp, College Station, TX). A 2-sided P value < 0.05 was considered statistically significant in all analyses.

RESULTS

A total of 238 eyes of 141 patients were included in this study, and 25 eyes (11%) of 16 patients were categorized as 10–2 CVF progressors. Demographic and clinical characteristics of eyes in the progressor and non-progressor groups were summarized in Table 1. No significant difference between the two groups was found for most clinical characteristics, including age, IOP measurements, percentage of pseudophakic eyes, distribution of baseline glaucoma severity, baseline 24–2 and 10–2 VF MD, and follow-up

duration (P > 0.05 for all). At the last visit, the progressors tended to have more severe glaucoma and worse VF MDs (P < 0.05 for all). For the macular OCT/OCTA parameters, as compared to progressors (mean [95%] wiVD = 37.2 [35.1, 39.4] %; wiGCC = 77.7 [74.2, 81.3] μm), non-progressors had significantly higher wiVD (mean [95%] = 40.8 [40.1, 41.5] %; P = 0.006) and thicker wiGCC (mean [95%] = 82.4 [80.9, 84.0] μm; P = 0.032).

The analysis of clinical variables associated with the rate of past 10–2 CVF worsening is presented in Table 2. In the univariable model, most clinical variables, including age, IOP measurements, baseline 10–2 MD, SSI, history of cataract surgery during follow-up, and follow-up duration, did not show statistically significant correlation (P > 0.05 for all) with the rate of 10–2 VF MD worsening. However, a lower wiVD (β [95% CI] = −0.02 [−0.03, −0.01]), a thinner wiGCC (β [95% CI] = −0.01 [−0.01, −0.00]), and a worse glaucoma severity (β [95% CI] = −0.30 [−0.46, −0.13]) were significantly associated with a faster past rate of CVF worsening (P < 0.05 for all). In the multivariable model, a lower wiVD remained significantly associated with faster past CVF MD worsening (β [95% CI] = −0.04 [−0.05, −0.02]; P < 0.001, R^2 = 0.32). Other significant contributors in this model included baseline 10–2 VF MD (β [95% CI] = −0.03 [−0.04, −0.01]), SSI (β [95% CI] = −0.01 [−0.02, −0.00]), and glaucoma severity (β [95% CI] = −0.40 [−0.59, −0.21]) (P < 0.05 for all). In the multivariable model including wiGCC, a thinner wiGCC also remained associated with a faster past CVF worsening (β [95% CI] = −0.01 [−0.01, −0.00]; R^2 = 0.21), as well as baseline 10–2 VF MD (β [95% CI] = −0.02 [−0.03, −0.01]) and glaucoma severity (β [95% CI] = −0.38 [−0.58, −0.19]) (P < 0.05 for all).

Table 3 shows the analysis of clinical variables associated with a past CVF progression event. In the univariable analysis, a lower wiVD (odds ratio [OR] [95% CI] = 1.15 [1.04, 1.27], per 1% lower), a thinner wiGCC (OR [95% CI] = 1.04 [1.00, 1.08], per 1μm thinner), and a worse glaucoma severity (OR [95% CI] = 5.43 [2.22, 13.28]) were significantly associated with increased odds of past CVF progression (P < 0.05 for all). Similar to the results of past rate of CVF worsening, no other clinical variables were significantly correlated with past CVF progression in the univariable models. In the multivariable analysis, after adjusting for age, SSI, baseline 10–2 VF MD, last-visit glaucoma severity, and mean IOP during follow-up, a lower wiVD remained associated with increased odds of past CVF progression (OR [95% CI] = 1.23 [1.06, 1.44] per 1% lower; P = 0.008). However, in the multivariable model evaluating OCT, wiGCC was no longer significantly associated with CVF progression (OR [95% CI] = 1.03 [0.99, 1.09] per 1μm thinner; P = 0.175). Baseline 10–2 VF MD (range of OR: 1.12–1.20) and glaucoma severity (range of OR: 8.83–11.52) also showed significant associations in the multivariable models (P < 0.05 for both).

DISCUSSION

This study examined the association of macular VD and GCC with 10–2 CVF progression in glaucoma. Lower measurements of both superficial wiVD and wiGCC were associated with faster rate of prior CVF worsening. Additionally, wiVD was more strongly associated with increased odds of past CVF progression event as compared to wiGCC. These findings

indicate the potential usefulness of macular OCT and OCTA measurements to identify glaucoma patients at greater risk of faster CVF progression.

In the current study, past rate of CVF worsening was significantly associated with both macular VD and GCC measurements. This finding is of particular clinical relevance, as it has been shown that the longitudinal trend of VF progression can be estimated based on VF results obtained from the earlier visits. In other words, the rate of prior VF worsening is indicative of the future rate of VF loss.[28] Furthermore, if appropriate intervention is not performed to alter the trajectory of progression, patients with faster past VF deterioration will likely continue to advance at a faster rate.[29] Considering the irreversible nature of glaucoma, it is therefore important for clinicians to assess the risk of VF progression when making treatment decisions. Our results suggest that macular VD and GCC may help assess glaucoma patients with faster CVF loss or at greater risk of further CVF progression, both of whom may require more intensive treatments and monitoring. Additionally, since the association with past rate of CVF worsening was directly examined, our findings may be particularly useful for early identification of high-risk cases when past data is not available or limited during the patient's first few encounters.

When analyzing the association of OCT/OCTA parameters with CVF progression event, macular VD remained significantly correlated after adjusting for potential confounders, while GCC was not. Although the differing nature of trend-based and event-based VF analysis may partially account for the discrepant results from that of past CVF worsening rate,[30 31] some prior studies provide other perspectives. Interestingly, in previous studies comparing OCT thicknesses and OCTA measurements for their functional association with VF and disease severity, a stronger correlation was usually found for VD.[32–37] Hou and colleagues reported a faster wiVD loss than wiGCC thinning in glaucoma eyes, with only wiVD correlating with disease severity.[32] In another recent study, Shin and colleagues reported that macular VD demonstrated a stronger correlation with CVF sensitivity compared to macular ganglion cell-inner plexiform layer thickness.[12] It is unclear if the weaker functional association of OCT is related to the inclusion of non-neuronal components in thickness measurements,[38] the more significant floor effect of OCT,[39 40] the stronger role of vascular factor in glaucomatous damage or CVF formation, [41 42] or the inherent less capability of thicknesses to reflect other physiological factors affecting visual function. Nevertheless, previous findings are consistent with our results showing a slightly stronger association between VD and CVF progression, as compared to that with thickness measurements. Still, it should be noted the reproducibility of OCTA is generally worse than OCT, which may limit its clinical utility.[43 44]

Although pertinent to the visual function and QoL,[8–11] studies on the structural-functional relationship between OCT/OCTA and CVF in glaucoma have been limited, with prior longitudinal studies focusing mostly on global VF progression. Consistent with our findings, a correlation between macular VD loss and CVF defect has been reported in some earlier cross-sectional OCTA studies.[12 13 45] As mentioned earlier, evidence has shown that glaucoma patients with faster past VF progression are more likely to show a faster rate of future progression, particularly when there are no modifying interventions. With the longitudinal study design, our findings add to the existing evidence suggesting

an association between OCT/OCTA changes and CVF defect,[12–16] and also provide insight into the pathophysiology of CVF loss. The significant association of macular VD with 10–2 CVF loss in both trend-based and event-based analysis supports the possible involvement of an alteration in the microvasculature in glaucoma.[2 46] While the clinical significance of the observed association remains to be determined, our study may serve as the basis for understanding the long-term relationship between structural damage and CVF progression, and for investigating the clinical application of OCT and OCTA in glaucoma risk assessment.

Limitations

There are some limitations in this study. First, VF testing is subjective and has greater variability than the structural measurements.[47–49] Thus, only eyes with at least 3 years of follow-up and five 10–2 VF tests were included to more reliably assess CVF worsening rate and CVF progression. Second, OCTA imaging is prone to artifacts, and the reliability of VD measurement depends heavily on the image quality.[46 50] For this reason, quality review was performed, and SSI was adjusted in all multivariable models. However, with the exclusion of unqualified OCTA images, the generalizability of results might be limited. Third, although significant association between OCT and OCTA parameters and CVF progression was found, whether it is strong enough to be clinically relevant requires further study. Last, since the number of CVF progressors was relatively small, it is possible that the study lacked sufficient power to detect significant associations for some clinical variables, including GCC. Future studies with more cases and longer follow-up are needed to confirm these observations.

In conclusion, lower macular VD and GCC were associated with faster worsening of the 10–2 CVF, and a lower macular VD was associated with increased odds of CVF progression. With macular OCT and OCTA, clinicians may better assess the risk of CVF progression in glaucoma eyes, as well as identify glaucoma patients with in need of more intensive treatment.

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e. Data availability:

The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

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SYNOPSIS

Lower macular VD and GCC were both associated with faster past 10–2 CVF worsening. A lower macular VD was more strongly associated with increased odds of past CVF progression event as compared to lower GCC.

KEY MESSAGE

- **What is already known on this topic** – CVF is pertinent to the quality of life. Although some cross-sectional studies have found a correlation between macular OCT/OCTA and CVF, longitudinal evidence remains lacking.
- **What this study adds** – In this longitudinal study, lower macular VD and GCC were both associated with faster past worsening of 10–2 CVF. Lower macular VD was also associated with increased odds of past 10–2 CVF progression event, while GCC was not.
- **How this study might affect research, practice or policy** – Through macular OCT/OCTA, clinicians might be able to identify glaucoma eyes with CVF progression.

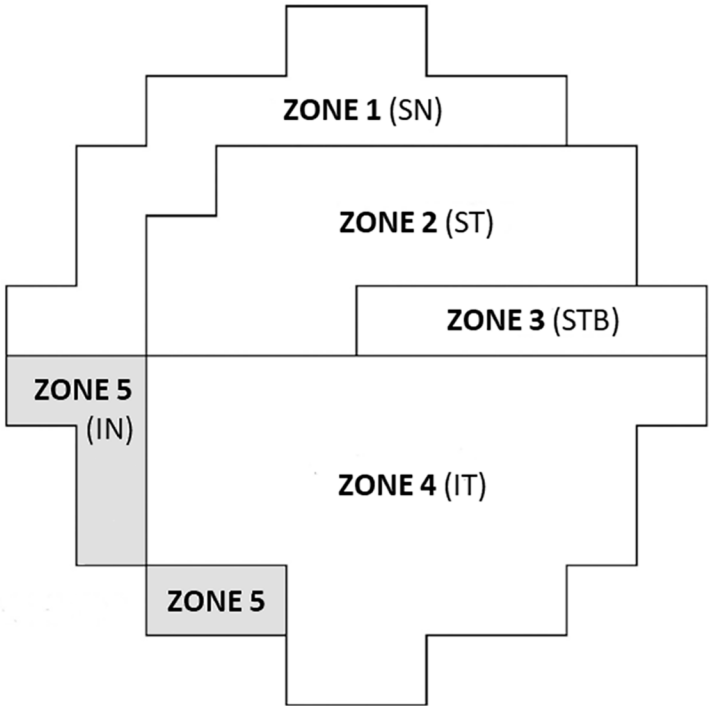

Figure 1.

10–2 Visual field (VF) zones defined based on their vulnerability to glaucomatous damage in the macula.[24] Each numbered zone corresponds to the following region: Zone 1 = superior nasal (SN); zone 2 = superior temporal (ST); zone 3 = superior temporal band (STB); zone 4 = inferior temporal (IT); zone 5 = inferior nasal (IN)

Table 1.

Demographics and Baseline Clinical Characteristics of the Subjects

	Progressors	Non-progressors	P value
Characteristic	**n = 25 eyes (16 subjects)**	**n = 213 eyes (125 subjects)**	
Age (years)	75.2 (69.2, 81.1)	72.5 (70.6, 74.4)	0.360
Gender (Female/ Male)	9/7	62/63	0.616
Race (African American/ non-African American)	3/13	34/91	0.469
Hypertension (Hypertensive/ non-hypertensive)	8/8	82/43	0.221
Diabetes (Diabetic/ non-diabetic)	3/13	17/108	0.578
Pseudophakic eyes (%) at baseline	9 (36)	57 (27)	0.644
Pseudophakic eyes (%) at last visit	11 (44)	78 (37)	0.934
Mean IOP during follow up (mmHg)	14.5 (13.2, 15.8)	14.7 (14.2, 15.2)	0.791
IOP at last visit (mmHg)	13.5 (12.0, 15.1)	14.5 (13.9, 15.0)	0.247
Axial length (mm)	24.3 (23.8, 24.7)	24.3 (24.1, 24.4)	0.975
CCT (μm)	529.5 (502.2, 556.8)	537.4 (531.5, 543.2)	0.555
Baseline 10-2 VF MD (dB)	−4.2 (−6.0, −2.3)	−3.1 (−3.8, −2.4)	0.310
Baseline 24-2 VF MD (dB)	−4.6 (−6.1, −3.1)	−3.6 (−4.3, −2.8)	0.250
Baseline glaucoma severity (Advanced/ early-moderate)	1/24	17/210	0.520
Last-visit 10-2 VF MD (dB)	−9.0 (−11.0, −7.1)	−3.0 (−3.7, −2.3)	**<0.001**
Last-visit 24-2 VF MD (dB)	−9.4 (−11.7, −7.2)	−4.1 (−4.8, −3.3)	**0.001**
Last-visit glaucoma severity (Advanced/ early-moderate)	9/16	20/207	**<0.001**
Whole-image GCC thickness (μm)	77.7 (74.2, 81.3)	82.4 (80.9, 84.0)	**0.032**
Whole-image VD (%)	37.2 (35.1, 39.4)	40.8 (40.1, 41.5)	**0.006**
OCT/OCTA SSI	58.1 (55.4, 60.9)	60.3 (59.2, 61.3)	0.142
Follow-up duration (years)	5.1 (4.7, 5.5)	5.0 (4.9, 5.1)	0.634

* Values are shown in mean (95% confidence interval), unless otherwise indicated.

Abbreviations: CCT, central corneal thickness; GCC = ganglion cell complex; IOP = intraocular pressure; MD = mean deviation; OCT = optical coherence tomography; OCTA = optical coherence tomography angiography; n = number; SSI = signal strength index; VD = vessel density; VF = visual field

Table 2.

Linear mixed model analysis of clinical variables associated with past rate of central visual field worsening

Variables	Univariable model		Multivariable model – OCTA		Multivariable model – OCT	
	β (95 % CI)	P value	β (95 % CI)	P value	β (95 % CI)	P value
Age, per 10 year older	−0.04 (−0.09, 0.01)	0.115	0.00 (−0.04, 0.04)	0.916	−0.03 (−0.17, 0.10)	0.634
Gender: female/male	0.07 (−0.04, 0.17)	0.226				
Race: African American/non-African American	0.09 (−0.03, 0.22)	0.133				
Axial length, per 100 mm longer	0.39 (−4.28, 5.07)	0.871				
CCT, per 100 μm thicker	0.09 (−0.03, 0.21)	0.130				
History of diabetes	−0.01 (−0.17, 0.15)	0.903				
History of hypertension	0.02 (−0.10, 0.13)	0.788				
IOP at last visit, per 1 mmHg higher	−0.00 (−0.02, 0.01)	0.848				
Mean IOP, per 1 mm Hg higher	0.00 (−0.01, 0.01)	0.957	0.02 (−0.01, 0.05)	0.783	0.02 (−0.01, 0.05)	0.242
Baseline 10-2 MD, per 1 dB higher	0.14 (−0.07, 0.36)	0.200	−0.03 (−0.04, −0.01)	**<0.001**	−0.02 (−0.03, −0.01)	**0.004**
Last-visit glaucoma severity: advanced/early-moderate	−0.30 (−0.46, −0.13)	**<0.001**	−0.40 (−0.59, −0.21)	**<0.001**	−0.38 (−0.58, −0.19)	**<0.001**
Cataract surgery during follow-up	0.00 (−0.01, 0.01)	0.759				
wiVD, per 1% lower	−0.02 (−0.03, −0.01)	**<0.001**	−0.04 (−0.05, −0.02)	**<0.001**		
wiGCC thickness, per 1 μm thinner	−0.01 (−0.01, 0.00)	**0.001**			−0.01 (−0.01, 0.00)	**0.004**
Follow-up duration, per 1 year longer	0.06 (0.00, 0.12)	0.066	0.05 (−0.01, 0.11)	0.074	0.04 (−0.02, 0.10)	0.163
Average SSI, per 1 unit higher	0.01 (0.00, 0.01)	0.149	−0.01 (−0.02, 0.00)	**0.031**	0.00 (−0.01, 0.01)	0.609

*Values are shown in β coefficient (95% CI). Negative β coefficient shows association with faster CVF loss.

**Statistically significant P values are shown in bold.

Abbreviations: CI = confidence interval; IOP = intraocular pressure; MD = mean deviation; wiGCC = whole-image ganglion cell complex; OCT = optical coherence tomography; OCTA = optical coherence tomography angiography; wiVD = whole-image vessel density

Table 3.

Linear mixed model analysis of clinical variables associated with past central visual field progression event

Variables	Univariable model		Multivariable model – OCTA		Multivariable model – OCT	
	Odds ratio (95 % CI)	P value	Odds ratio (95 % CI)	P value	Odds ratio (95 % CI)	P value
Age, per 1 year older	1.01 (0.97, 1.05)	0.652	0.99 (0.95, 1.03)	0.598	1.00 (0.96, 1.04)	0.983
Gender: female/male	1.03 (0.42, 2.56)	0.943				
Race: African American/non-African American	0.53 (0.14, 2.00)	0.351				
Axial length, per 1 mm longer	1.02 (0.71, 1.46)	0.921				
CCT, per 1 μm thicker	1.00 (0.99, 1.01)	0.718				
History of diabetes	1.59 (0.57, 4.44)	0.379				
History of hypertension	0.59 (0.23, 1.48)	0.259				
IOP at last visit, per 1 mmHg higher	0.94 (0.85, 1.04)	0.237				
Mean IOP, per 1 mm Hg higher	0.99 (0.89, 1.09)	0.791	0.95 (0.84, 1.07)	0.428	0.95 (0.85, 1.07)	0.431
Baseline 10-2 MD, per 1 dB higher	0.97 (0.92, 1.02)	0.242	1.20 (1.06, 1.35)	**0.003**	1.12 (1.00, 1.25)	**0.041**
Last-visit glaucoma severity: advanced/early-moderate	5.43 (2.22, 13.28)	**<0.001**	11.52 (2.73, 48.71)	**<0.001**	8.83 (2.03, 38.50)	**0.004**
Cataract surgery during follow-up	0.59 (0.07, 4.94)	0.628				
wiVD, per 1% lower	1.15 (1.04, 1.27)	**0.006**	1.23 (1.06, 1.44)	**0.008**		
wiGCC thickness, per 1 μ thinner	1.04 (1.00, 1.08)	**0.035**			1.03 (0.99, 1.09)	0.175
Follow-up duration, per 1 year longer	1.12 (0.71, 1.77)	0.637				
Average SSI, per 1 unit higher	0.96 (0.92, 1.00)	0.120	1.03 (0.96, 1.12)	0.392	0.97 (0.91, 1.02)	0.251

*Statistically significant P values are shown in bold.

Abbreviations: CI = confidence interval; IOP = intraocular pressure; MD = mean deviation; wiGCC = whole-image ganglion cell complex; OCT = optical coherence tomography; OCTA = optical coherence tomography angiography; wiVD = whole-image vessel density