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Retinal and choroidal morphometric analysis in fellow eye of unilateral wet age related macular degeneration using optical coherence tomography angiography

Sudha Ranabhat^{1*} , Kiran Shakya¹, Priya Bajgai¹, Lazza Singh¹, Shreeji Shrestha¹ and Roshni Agrawal²

Abstract

Background Age-related macular degeneration (AMD) when associated with macular neovascularization can cause severe visual morbidity. This study aims to evaluate the retinal and choroidal microvascular alterations using optical coherence tomography angiography (OCTA) in eyes with unilateral wet age-related macular degeneration (AMD) termed as “affected eye” (AE) and compare it with their “fellow eyes” (FE).

Methods This cross-sectional study included 60 patients (120 eyes) with age over 50 years. Vessel density (VD), perfusion density (PD), and foveal avascular zone (FAZ) in the superficial capillary plexuses (SCP), deep capillary plexus (DCP) and avascular slab were assessed using OCTA. Enhanced depth imaging was used to evaluate subfoveal choroidal thickness (SFCT) and choroidal vascularity index (CVI).

Results The mean age was 73.9 ± 9.54 years (51–89 years) with 51.7% male. Quantitative OCTA analysis showed no significant inter-eye differences in VD or PD in SCP or DCP ($p > 0.05$). However, FAZ was significantly enlarged in AE compared with FE in SCP (0.91 ± 0.40 vs. 0.64 ± 0.20 mm²; $p < 0.001$) and DCP ($p < 0.001$). FAZ enlargement in the avascular slab was not statistically significant ($p = 0.20$). Pattern I macular neovascularization (MNV) was significantly associated with the shape ($p = 0.026$), presence of anastomoses ($p = 0.029$), and overall activity scores ($p = 0.001$). Inter-eye differences choroidal parameters were statistically significant for SFCT ($p = 0.019$), haller layer ($p = 0.014$) and CVI ($p < 0.001$). AE status was significantly associated with age ($p = 0.04$) smoking ($p = 0.01$), and lens status ($p = 0.05$).

Conclusion FAZ enlargement demonstrated greater inter-eye separation and higher discriminatory performance compared than density-based OCTA parameters and may reflect localized microvascular or structural alteration in unilateral neovascular AMD. OCTA-based assessment of FE may aid in detecting early microvascular alterations and guiding timely intervention, which may be potentiated by retinal and choroidal vascular or structural remodeling.

Keywords Age related macular degeneration, Choroidal vascular index, Choroidal neovascular membrane, Enhanced depth imaging, Foveal avascular zone, Macular neovascularization, Optical coherence tomography angiography, Perfusion density, Vessel density

*Correspondence:
Sudha Ranabhat
sudharanabhat05@gmail.com

¹Department of Vitreoretina, Nepal EyeHospital, Kathmandu, Nepal

²Department of Ophthalmology, National Academy of medical Sciences, Kathmandu, Nepal



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Introduction

Age-related macular degeneration (AMD) is a leading cause of vision loss in elderly, which rises exponentially when complicated by macular neovascularization (MNV) [1, 2]. AMD affects approximately 10% over 65 years, and increases to 25% after 75 years. In our region, it is the fourth leading cause of blindness with a prevalence of 5.3% [3]. It is a multifactorial disease, with age, genetics, race, gender, smoking, nutrition plays established roles, however the contribution of systemic co-morbidities remains controversial [4, 5].

AMD is broadly classified as dry and wet type. Dry AMD occurs with drusen accumulation and retinal pigment epithelium (RPE) dysfunction.[6]Wet AMD is caused by abnormal neovascular growth from the choriocapillaris causing subsequent leakage/hemorrhage leading to serous RPE detachment provoking scar.[7,8] Alteration of choroidal perfusion, vessel density and thickness are crucial for disease pathogenesis [9, 10, 11]. Although neovascular AMD is primarily characterized by abnormalities of the choroid, RPE, and choroidal neovascularization, increasing evidence suggests that retinal microcirculation may also be altered. Optical Coherence Tomography angiography (OCTA) studies have demonstrated changes in retinal vessel density and foveal avascular zone (FAZ), suggesting that retinal vascular remodeling may accompany disease progression [6, 12]. The fellow eye of unilateral neovascularAMD (nAMD) often shares systemic, genetic, and local microvascular risk factors. Evaluation of retinal circulation may help identify subclinical alterations before overt neovascular conversion occurs. Studies have shown that, FE carries a risk of progression, with reported conversion rates ranging from approximately 10–15% at 1 year and 30–40% over 5 years, depending on baseline risk factors such as drusen burden, pigmentary abnormalities, and Optical Coherence Tomography (OCT) and OCTA biomarkers [12, 13].

OCTA enables non-invasive, depth resolved visualization of retina and choroidal microcirculation, allowing detailed assessment of superficial, deep capillary plexuses, choriocapillaris and FAZ.[14,15,16,17]It has a significant advantage with blood flow visualization, therefore areas of choroidal ischemia, microvascular changes, precise localization and delineation of the lesion can be made [15, 17, 18]. Enlargement of the FAZ reflects reduced capillary perfusion and disruption of retinal microvascular integrity, which may precede clinically detectable structural changes [15, 16]. This aids in earlier disease identification and enhances the effectiveness of recent treatments [19, 20].

nAMD is traditionally considered a disorder involving the RPE, Bruch's membrane, and choroidal circulation. However, increasing evidence suggests that

microvascular and structural alterations may extend beyond clinically active lesions and may also be present in the apparently unaffected fellow eye (FE). Since FE of unilateral nAMD patients share common genetic, systemic, and local environmental influences, evaluation of inter-eye differences may provide insight into early disease-related alterations preceding overt neovascular conversion.

Although previous OCTA studies have reported vascular alterations in AMD, most investigations have focused either on retinal microcirculation or choroidal characteristics independently and frequently involved comparisons across different individuals. Data integrating retinal OCTA metrics and quantitative choroidal morphometry within a paired-eye design remain limited, particularly in treatment-naïve unilateral nAMD. The present study aimed to minimize inter-individual and systemic vascular variability while evaluating whether retinal and choroidal changes demonstrate differential sensitivity to disease expression. The rationale of this study was to investigate whether clinically unaffected FE of unilateral nAMD patients demonstrate subclinical retinal microvascular and choroidal structural alterations detectable by OCTA and, thereby improving understanding of early disease-related changes beyond overt neovascular lesions.

Materials and methods

This was a cross-sectional, hospital-based study conducted for a duration of one year in Retina clinic of Nepal Eye Hospital, Tripureshwor, including all the treatment naïve, consecutive patients above 50 years with evidence of unilateral wet AMD termed as “Affected eyes” (AE) and their FE. The FE was defined as the contralateral eye without evidence of neovascular (exudative) AMD. FE were required to have no macular neovascularization, intraretinal fluid, subretinal fluid, hemorrhage, or other signs of active exudation on clinical examination, OCT, and OCTA. Non-exudative AMD changes, including drusen and/or retinal pigment epithelium (RPE) abnormalities, were permitted. A total of 75 patients were examined, however the patients with presence of wet AMD in both eyes were excluded and only 60 patients (120 eyes) were included. The diagnosis of wet AMD in the (AE) was based on clinical examination, enhanced depth imaging (EDI) OCT and OCTA. Diagnostic features included the presence of MNV, intraretinal fluid (IRF), subretinal fluid (SRF), pigment epithelial detachment (PED), subretinal hyperreflective material, or evidence of exudative activity attributable to AMD. MNV was classified according to the Consensus on Neovascular AMD Nomenclature (CONAN): Type 1 MNV as sub-RPE neovascularization, Type 2 MNV as subretinal neovascularization, Type 3 MNV as retinal angiomatous proliferation/intra-retinal neovascularization, and disciform scar as fibrotic

end-stage lesion [21]. On OCTA, the eyes with MNV showed the scans of the outer retinal layer with a vascular network, where flow signals are normally absent. When outer retinal slabs showed faint flow signal, choroidal slabs were used as a reference. Exclusion criteria were maculopathy secondary to causes other than AMD. Diabetic and hypertensive patient included did not have maculopathy associated with the systemic diseases. High myopia (spherical equivalent > 6 diopters, axial length ≥ 26.0 mm), glaucoma, ocular trauma, past intraocular surgeries of < 6 months, patients with solid organ transplants, patients under any treatment that lead to potential independent effects on the retinal microvasculature, poor OCTA images with a signal strength index (SSI) less than 50 due to motion artifacts or media opacities and disability to cooperate with image acquisition. Informed written consent was obtained prior to the enrollment. This study adhered to the tenant of the declaration of Helsinki and was approved by the institutional review committee of National Academy of Medical Sciences, Bir Hospital with reference number 33/2082/83.

Detailed clinical history including age, gender, presence of systemic disorders was taken. The ophthalmologic examination included best corrected Snellen visual acuity (BCVA). Slit lamp bio-microscopy (Haag-Streit BQ 900, HAAG - STREIT AG, Koniz, Switzerland) of anterior as well as dilated posterior segment using 90 D and 20 D biconvex lens (Volk Optical Inc. USA) was performed.

Each subject underwent OCTA imaging (OCTA; Spectralis OCTA, Heidelberg Engineering, Heidelberg, Germany) of both the eyes by the same examiner (OP). Light source used by this device was 870 nm superluminescent diode, providing A scans at a speed of 85,000 per second and the maximum scan depth was approximately 1.9 mm. Axial resolution was 3.9 μm and lateral resolution 6 μm . Scan pattern used was 6*6 mm for quantitative analysis of macular perfusion and choriocapillaris flow with A scan density of 512*512 pixels. The system employed the full spectrum amplitude decorrelation algorithm for generating angiographic flow images. For correcting the motion artifact between the consecutive images, TrueTrack active eye tracking and motion correction technology was utilized.

Automated layer segmentation was performed using the Heidelberg Eye Explorer (HEYEX) software initially and segmentation boundaries were subsequently reviewed by two masked graders and manual correction was performed whenever segmentation errors were identified. Superficial capillary plexus (SCP) was segmented between internal limiting membrane (ILM) to outer boundary of the inner plexiform layer (IPL). Deep capillary plexus (DCP) was segmented between an inner boundary of the IPL and outer boundary of the outer PL (OPL). Vessel density (VD) and perfusion

density (PD) was performed for SCP, DCP centering the parafovea. For quantitative analysis the region of interest (ROI) consisted of entire OCTA scan of 6*6 mm, images were imported to ImageJ (National Institutes of Health, Bethesda, USA). Images were converted to 8-bit, phansalkar local thresholding was done followed by binarization of the image then VD and PD were calculated with predefined ROI, also shown in Fig. 1 (a-c). FAZ perimeter was measured using the polygonal tool and was measured using Heidelberg OCTA predefined segmentation slabs, including the SCP, DCP, and avascular slab outputs. Image processing and quantitative morphometric measurements were performed using ImageJ (National Institutes of Health, Bethesda, USA).

As a secondary exploratory analysis, qualitative OCTA characteristics of MNV were assessed to describe lesion morphology and activity in the affected eyes. These analyses were independent of the primary quantitative comparisons between affected and fellow eyes. The OCTA biomarkers of choroidal neovascularization (CNV) morphology was documented as described by Coscas et al. [22] Five criteria were considered to determine the pattern of MNV: shape, vessel branching, presence of anastomoses and loops, morphology of the vessel termini, presence of a perilesional hypointense halo (flow impairment, steal or localized atrophy). If a MNV lesion showed at least three of these features, it was assessed as Pattern I (active-recent lesion) and if it showed less than three criteria, it was considered as Pattern II (mature lesion).

A 1500- μm wide region centered on the fovea was selected from the outer border of the RPE to the inner scleral interface. The image was converted to 8-bit, and binarization was performed using Niblack's auto local thresholding and the total choroidal area (TCA) area was observed by measuring the luminal area (LA), color threshold was applied, and the CVI was computed as $(\text{LA}/\text{TCA}) \times 100$ as shown in Fig. 1 (d-f). All OCTA segmentations and EDI measurements were manually reviewed by two masked graders to ensure image quality and segmentation accuracy. Any discrepancies were resolved through consensus review. Enhanced Depth Imaging OCT (EDI OCT) (Heidelberg Engineering, Heidelberg, Germany) was subfoveal choroidal thickness (SFCT) was measured as the vertical distance from the outer border of the RPE-Bruch membrane complex to the choroid-scleral interface. Haller layer thickness was defined as the distance from the choroid-scleral interface to the innermost border of large-caliber choroidal vessels, while Sattler layer thickness was defined as the thickness of the medium-vessel layer between the choriocapillaris and Haller layer and were recorded in micrometer (μm).

For statistical purposes, BCVA was converted to the logarithm of the minimal angle of resolution (log MAR).

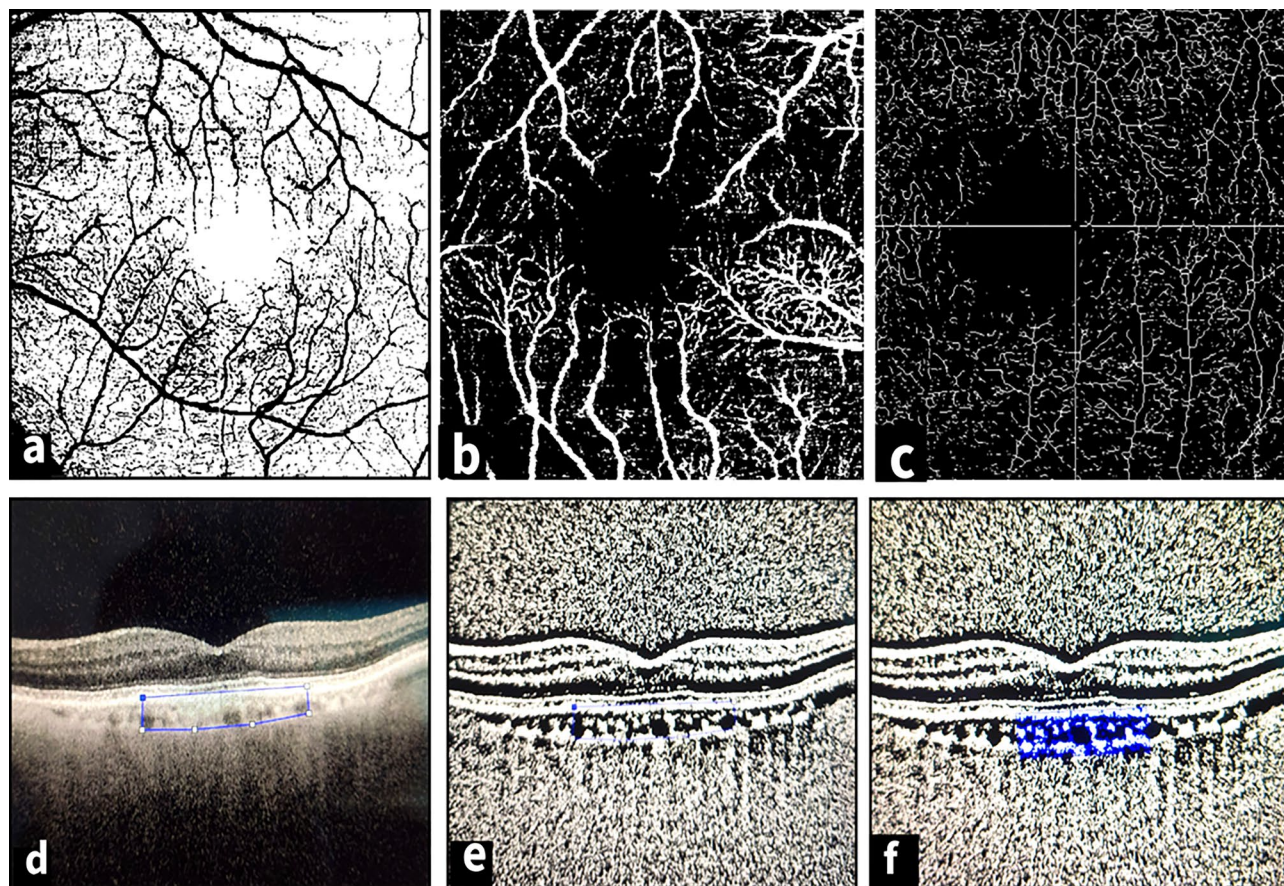


Fig. 1 showing workflow for quantitative retinal and choroidal image analysis. (a–c) En face 6*6 mm, OCTA image processing showing vascular segmentation and quantitative assessment of retinal microvascular parameters. (a) OCTA image of SCP converted to 8-bit, (b/c) phansalkar local thresholding was done for the OCTA image of DCP followed by binarization of the image, VD and PD were calculated with predefined ROI. (d) Selection of the subfoveal choroidal region of interest (1500 μm) on EDI OCT and converted to 8-bit. (e) Image binarization and local thresholding with Niblack performed in ImageJ to separate vascular and stromal components. (f) Extraction of the luminal and total choroidal area used for calculation of choroidal vascularity index (CVI=luminal choroidal area / total choroidal area × 100)

Data was entered and analyzed using SPSS software (version 20, IBM Corp., Chicago, IL, USA). Descriptive statistics like means and standard deviation was applied for continuous variable. The significance of vessel density, perfusion density and FAZ perimeter was evaluated by paired t test. Correlation between OCTA parameters and choroidal thickness, age was assessed using Pearson's or Spearman's correlation coefficients. After the analysis, a p-value < 0.05 was considered statistically significant.

Results

A total of 60 patients (120 eyes) with unilateral wet AMD were included with a mean age 73.9 ± 9.54 years (51–89 years). Male comprised 51.7% (n 31) and female were 48.3% (n 29). History of smoking was present in 63.3% (n 38). Systemic co-morbidities were present in 46.7% (n 28), most common was hypertension in 21.7% (n 13), type II diabetes mellitus in 18.4% (n 11), coronary artery disease in 3.4% (n 2), dyslipidemia in 1.7% (n 1)

and chronic obstructive pulmonary disease in 1.7% (n 1). Mean visual acuity of affected eyes (AE) was 1.28 ± 0.50 and FE was 0.75 ± 0.59 . Lens status as well as the fundus findings of the affected and the fellow eye is mentioned in Table 1.

The most common MNV morphological pattern was glomerular in 35% (n 21) followed by seafan in 25% (n 15), dead tree in 25% (n 15), medusa head in 13.3% (n 8) and filament in 1.6% (n 1). The morphological patterns are shown in Fig. 2.

Pattern I MNV (active) was observed in 75% (n 45) whereas Pattern II MNV (inactive) in 25% (n 15). Pattern I MNV showed a significant association with lesion shape (p 0.026), presence of anastomosis (p 0.029), and higher overall activity score (p 0.001). Perilesional halo (p 0.15), vessel branching (p 0.17) and peripheral arcade (p 0.14) did not demonstrate significant association with MNV activity.

Table 1 showing status of the lens and fundus findings

Parameters		Affected Eyes		Fellow Eyes	
		N	%	N	%
Lens	Clear	3	5.1	3	5.1
	CC	6	10.2	5	8.5
	NS	24	40.8	24	40.8
	PSCC			3	5.1
	PCIOL	27	45.9	25	42.5
Fundus Findings	Normal			27	45
	Dry AMD			33	55
	MNV I	21	35		
	MNV II	28	46.6		
	MNV III	5	8.3		
	Disciform Scar	6	10		

AMD Age relate macular degeneration, CC Cortical cataract, MNV Macular neovascularization, NS Nuclear sclerosis, PCIOL Posterior chamber intraocular lens, PSCC Posterior sub capsular cataract

Quantitative OCTA analysis revealed modest inter-eye differences in VD and PD, with the affected eye demonstrating slightly reduced SCP VD (AE $16.2 \pm 9.7\%$ vs. FE $18.5 \pm 13.1\%$) and PD (AE $5.66 \pm 3.0\%$ vs. FE $6.15 \pm 3.6\%$) (Table 2), however, these differences were not statistically significant (VD: $p=0.28$; PD: $p=0.41$). DCP values were nearly identical between eyes for VD (AE $18.7 \pm 5.6\%$ vs. FE $19.1 \pm 5.8\%$; $p=0.65$) and PD (AE $7.74 \pm 3.1\%$ vs. FE $7.99 \pm 4.0\%$; $p=0.69$). In contrast, FAZ metrics demonstrated pronounced differences, with the AE exhibiting larger SCP FAZ (AE $0.91 \pm 0.40 \text{ mm}^2$ vs. FE $0.64 \pm 0.20 \text{ mm}^2$; $p<0.001$). The paired t-test results while comparing AE with FE showed VD (t value -1.122), PD (t value -0.95) and FAZ (t value 4.85) in the SCP. DCP showed VD (t value -0.65), PD (t value -0.43) and FAZ (t value 3.64), and avascular slab FAZ was (t value 1.283). Significant FAZ enlargement is observed in both the SCP ($p<0.001$) and DCP ($p<0.001$), whereas avascular slab FAZ did not reach significant level ($p=0.20$) as shown in Table 2.

ROC analysis was performed to further evaluate the discriminatory ability of each OCTA parameter, in which SCP FAZ achieved the highest discriminatory performance (AUC=0.729), followed by DCP FAZ (AUC=0.658), whereas avascular slab FAZ showed lower discriminatory ability (AUC=0.586). VD and PD parameters demonstrated limited discrimination, SCP VD (AUC=0.551), SCP PD (AUC=0.533), DCP VD (AUC=0.507) and DCP PD (AUC=0.511) as shown in Fig. 3.

Inter eye clinical significance discrimination map was performed, where VD and PD measurements showed a reduction in aAE compared with FE. The relative inter-eye difference observed in SCP VD was 12.4% decrease; $p=0.28$, followed by SCP PD 8.0% decrease; $p=0.41$, whereas DCP VD 2.1% decrease; $p=0.65$ and DCP PD 3.1%

decrease; $p=0.69$. In contrast, SCP FAZ area demonstrated a larger increase in AE which is 42.2% larger than FE.

Choroidal parameters including SFCT, Haller layer thickness, Sattler layer thickness, and choroidal vascularity index (CVI) were performed for AE and FE. Inter-eye differences in these parameters were statistically significant for SFCT ($p=0.019$), haller layer ($p=0.014$) and CVI ($p<0.001$) are summarized in Table 3.

Pearson correlation analysis demonstrated no significant relationship between age and FAZ measurements in either AE and FE. SCP FAZ showed negligible correlation with age in AE ($r=-0.009$, $p=0.946$) and FE ($r=-0.008$, $p=0.952$). Similarly, DCP FAZ demonstrated no significant association with age in AE ($r=-0.070$, $p=0.595$) and FE ($r=0.168$, $p=0.200$). Measurements from the avascular slab also showed no significant age-related association with AE ($r=0.036$, $p=0.785$) and FE ($r=0.197$, $p=0.132$).

Discussion

This prospective paired-eye OCTA study evaluated retinal and choroidal micro-vasculature in patients with unilateral wet AMD, with particular emphasis on differences between the AE and the FE. One of the key finding of our study is FAZ enlargement, particularly in the SCP and DCP, distinguishing AE from FE. Among the evaluated OCTA biomarkers, SCP FAZ demonstrated the strongest discriminatory performance (AUC=0.729), suggesting that FAZ enlargement may serve as a quantitative marker than density-based metrics for detecting subtle inter-eye microvascular alterations in unilateral wet AMD. As FAZ, is a marker of parafoveal capillary loss, impaired autoregulation, and altered retinal architecture, which contributes to photoreceptor and RPE dysfunction. Macular involvement in AMD is characterized primarily by central capillary disruption and structural remodeling rather than diffuse microvascular density loss, a pattern previously described in OCTA-based AMD studies [1, 2, 6]. FAZ measurements is less affected by projection artifacts and segmentation variability and its enlargement may reflect early retinal microvascular compromise. This could represent a biomarker of subclinical changes in the fellow eye before overt neovascular conversion.

VD and PD in both SCP and DCP were only marginally reduced in AE and did not reach statistical significance. This observation aligns with prior reports indicating that global density metrics may be relatively insensitive in AMD, partly due to compensatory vascular remodeling, segmentation inaccuracies, and masking effects from exudation or hemorrhage.[1, 6, 16].

Fellow eye as a window to early disease

Paired-eye design is another strength of this study, that are controlled for systemic and demographic confounders. Although FE were non-exudative, OCTA parameters

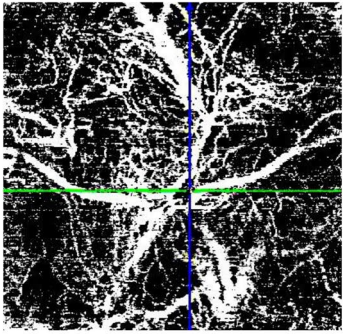
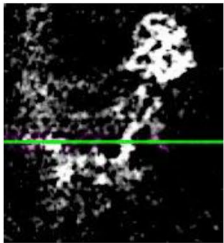
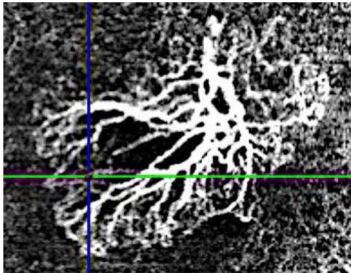
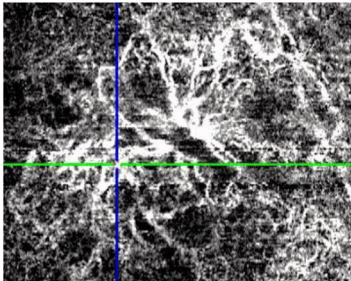
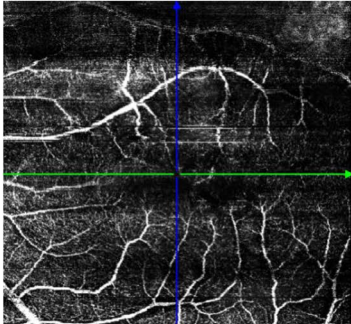
A	Dead Tree	
B	Glomerular	
C	Seafan	
D	Medusa head	
E	Filament	

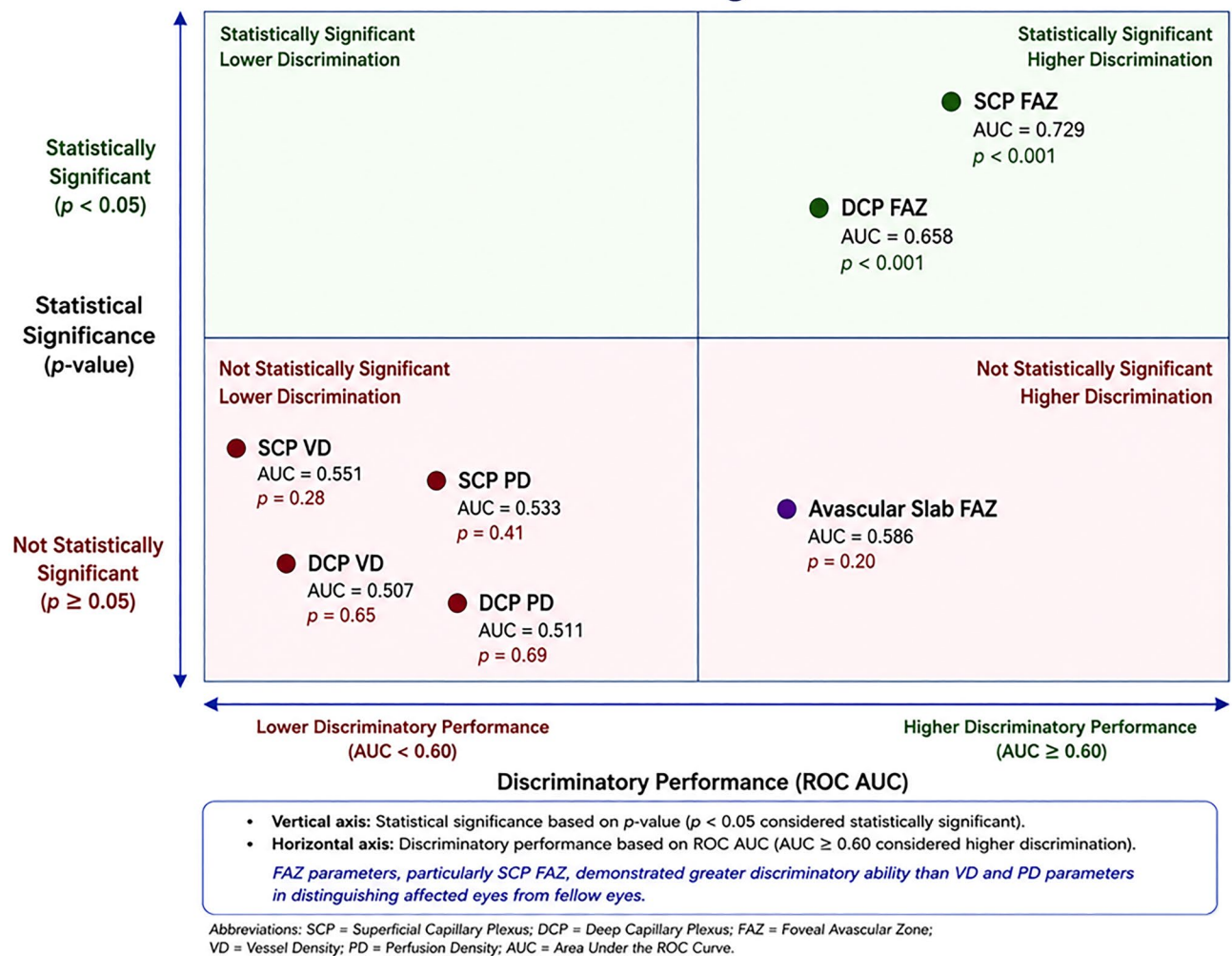
Fig. 2 showing different MNV morphological patterns

Table 2 showing vessel density, perfusion density and FAZ of Affected eyes and their fellow eye

	SCP			DCP			Avascular slab
	VD (%)	PD (%)	FAZ (mm ²)	VD (%)	PD (%)	FAZ (mm ²)	FAZ (mm ²)
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Affected eye	16.2 ± 9.7	5.66 ± 3	0.91 ± 0.4	18.7 ± 5.6	7.74 ± 3.1	0.56 ± 0.3	0.24 ± 0.1
Fellow eye	18.5 ± 13.1	6.15 ± 3.6	0.64 ± 0.2	19.1 ± 5.8	7.99 ± 4	0.42 ± 0.1	0.21 ± 0.1
p value	0.28	0.41	< 0.001	0.65	0.69	< 0.001	0.20
t- value	-1.222	-0.95	4.85	-0.65	-0.43	3.64	1.283

DCP deep capillary plexus, FAZ foveal avascular zone, PD perfusion density, SCP superficial capillary plexus, VD vessel density

OCTA Parameter Significance Matrix

**Fig. 3** OCTA parameter significance matrix

clustered in a zone of high clinical discrimination, could be an indication of subtle microvascular alterations. This supports the concept that AMD is a bilateral disease with asymmetric clinical expression, and FE of unilateral wet AMD has early biomarker potential, as it represents a preclinical disease stage as demonstrated by previous studies [9, 20, 23]. However, because of the cross-sectional design and the absence of a healthy control group, the present study cannot determine whether

the observed alterations precede neovascular conversion or represent early biomarkers of disease. Prospective longitudinal studies including age- and systemic factor-matched healthy controls are required to validate these findings.

Histopathological study performed by Seddon et al., further supports bilateral choriocapillaris loss even in eyes without clinically evident neovascularization, reinforcing the biological plausibility of our findings.¹¹ The

Table 3 showing choroidal parameters of Affected and Fellow eye

Parameters	Sattler Layer (μm)	Haller Layer (μm)	Sub-foveal Choroidal Thickness (μm)	Choroidal Vascular Index (%)
Affected eye	65 ± 30	99.8 ± 37.2	165 ± 62.2	39.1 ± 5.59
Fellow eye	70.9 ± 29	110 ± 41.5	181 ± 64.6	58.95 ± 5.36
p value	0.098	0.014	0.019	< 0.001
T score	−1.68	−2.54	−2.41	−16.55

AE is significantly associated with older age (mean age 73.9 ± 9.54 years; p 0.04), smoking (smokers 63.3%; p 0.01) and lens status differed between groups (Phakic 57.5%, pseudophakic 42.5%; p 0.05). Other parameters such as gender (male 51.7%, female 48.3%; p 0.35), race (p 0.93), and co-morbidities (Nil 53.3%, comorbidities present in 46.7%; p 0.1) did not have any association with AE

observed inter-eye differences in FAZ and choroidal parameters suggest that FE may harbor subclinical alterations and routine OCTA surveillance of FE is important for tracking the disease progression; however, this study was not designed to establish these changes as markers of early AMD. Previous longitudinal studies have demonstrated a substantial risk of FE as high as 54% in 10 years after the diagnosis in the exudative eye, supporting careful surveillance of the FE in high-risk patients [25, 26]. OCTA may complement structural OCT by detecting microvascular abnormalities before overt exudation, although prospective studies are needed to determine its role in routine surveillance.

nAMD is traditionally not classified as a retinal ischemic disease, however studies suggests that retinal microvascular alteration may occur in association with disease activity. OCTA studies have reported FAZ enlargement in eyes with active nAMD. These changes are thought to reflect secondary rather than primary ischemic mechanisms. One possible explanation is that intraretinal fluid (IRF) causes mechanical separation and distortion of retinal tissue, which may compress capillary networks and impair perfusion. In addition, IRF may disrupt neurovascular coupling by altering oxygen diffusion and increasing metabolic mismatch within the inner retina. Subretinal fluid (SRF) may contribute indirectly through photoreceptor dysfunction and retinal remodeling, although its direct effect on retinal capillary flow is less established than that of IRF [24, 27]. Furthermore, inflammatory mediators and VEGF overexpression associated with active neovascularization may alter retinal vascular permeability and local hemodynamics. Therefore, retinal microcirculation changes observed on OCTA in nAMD may represent secondary microvascular remodeling related to exudation and retinal structural changes rather than classical retinal ischemia [24, 28].

Choroidal structural and vascular alterations

Choroidal assessment demonstrated statistically significant inter-eye differences in SFCT, Haller layer thickness,

and CVI. These findings are consistent with growing evidence that choroidal vascular insufficiency plays a crucial role in AMD pathogenesis, particularly in the development of neovascular complications [10, 11]. CVI has emerged as a more stable and physiologically meaningful parameter than choroidal thickness alone, as it reflects the proportion of vascular luminal area within the choroid and is less influenced by age or diurnal variations [10, 11]. The significantly lower CVI observed in AE in our study supports prior reports linking reduced choroidal vascularity with ischemia-driven VEGF upregulation and MNV formation [10, 11].

MNV morphology and activity

Qualitative OCTA analysis was performed as a secondary analysis to characterize the neovascular lesions within the study cohort and to place the quantitative findings in the context of lesion activity. Pattern I (active) MNV was significantly associated with lesion shape, presence of anastomoses, and higher activity scores. These findings closely mirror the OCTA-based MNV activity criteria described by Coscas et al., who highlighted the diagnostic value of vascular complexity and anastomotic loops in identifying disease activity [22]. Jia et al. also demonstrated that OCTA can non-invasively delineate MNV architecture and quantify lesion activity [15, 16]. This further enhances its role in disease monitoring and therapeutic interventions, particularly in assessing treatment response and recurrence. However, the number of inactive neovascular lesions were relatively small (25%, n 15). Therefore, subgroup comparisons should be interpreted cautiously, as limited sample size may reduce statistical power and restrict generalizability of the findings. Larger studies with more balanced representation of active and inactive lesions are required to validate these observations.

Age-related retinal and choroidal thinning is a recognized physiological process and may influence retinal microvascular. Previous OCTA studies have demonstrated that FAZ tends to increase with advancing age, likely due to progressive capillary rarefaction and reduced retinal perfusion. Therefore, age may act as a confounding factor when interpreting FAZ enlargement [29, 30]. However, the magnitude of FAZ enlargement observed in our AE exceeds the subtle changes generally attributed to normal aging alone and significant association was not observed between age and FAZ measurements, suggesting that disease-related microvascular remodeling may contribute to the observed differences. Future longitudinal studies with age-adjusted analysis are needed to determine whether FAZ enlargement independently predicts AMD progression.

AE was significantly associated with age and smoking history, which are well-established risk factors [4, 5, 8].

Smoking is known to promote oxidative stress, endothelial dysfunction, and choroidal vascular damage accelerating the AMD progression [4, 5]. Although lens status was recorded as a baseline clinical characteristic, its clinical relevance to OCTA and choroidal measurements could not be established in the present study. The association with lens status may reflect age-related factors or improved imaging quality in patients without cataract. Since age and image quality were not adjusted for and no healthy control group was included, the observed association should be interpreted cautiously. Future studies with appropriate adjustment for imaging-related confounders are warranted. Other systemic co-morbidities did not show significant associations, consistent with the heterogeneous results reported in previous epidemiological studies.[4, 8].

Systemic vascular conditions such as hypertension, diabetes mellitus, and dyslipidemia are recognized contributors to retinal and choroidal vascular alterations and may influence OCTA parameters as shown by multiple studies [31, 32]. Although patients with diabetic retinopathy or diabetic maculopathy were excluded, diabetes itself may produce subclinical retinal microvascular changes, including alterations in FAZ and capillary density, before clinically detectable retinopathy develops. While the paired-eye design partially controls for systemic exposures by comparing both eyes of the same individual, residual confounding related to diabetes and other systemic vascular conditions cannot be completely excluded. Therefore, interpretation of retinal vascular findings should be made cautiously.

Clinical implications

The findings of this study reinforces the clinical role of OCTA in AMD management. FAZ enlargement demonstrated greater discriminatory performance than VA and PD in this cohort and may reflect localized microvascular remodeling or altered foveal architecture. FAZ measurements could have captured localized structural or perfusion-related changes that are not reflected by global density metrics. Our findings support the potential role of OCTA as an adjunctive imaging modality for evaluating FE of patients with unilateral neovascular AMD. Previous studies have shown that OCTA can detect subclinical neovascular complexes and microvascular alterations before clinical conversion. However, prospective longitudinal studies are required before OCTA biomarkers can be incorporated into routine risk stratification.

The limitations of this study include its cross-sectional design, which precludes assessment of longitudinal disease progression and conversion of FE to neovascular AMD. Furthermore, the absence of a healthy age-matched control limited our ability to distinguish AMD-related changes from physiological aging or

systemic vascular influences. Future longitudinal studies incorporating healthy controls and serial OCTA imaging are required to determine the predictive significance of these imaging biomarkers. As OCTA remain susceptible to motion artifacts and segmentation errors despite stringent image quality control, isolated statistically significant findings should be interpreted cautiously and require validation in larger independent cohorts. Severity and duration of systemic vascular comorbidities were not quantified or adjusted in the present analysis, which may have influenced retinal and choroidal measurements. Another limitation is the formal interobserver reproducibility analysis (intraclass correlation coefficient) was not performed. Future studies should include quantitative repeatability assessment to strengthen measurement reliability.

In conclusion, this study demonstrates that FAZ enlargement is a sensitive OCTA parameter distinguishing AE from FE in unilateral wet AMD, while reduced SFCT and CVI highlight underlying choroidal vascular insufficiency. OCTA-based assessment of FE provides valuable insights into early microvascular alterations and may play a pivotal role in early detection, monitoring, and prevention of vision-threatening disease progression. The novelty of the present study lies not in demonstrating that vascular alterations occur in AMD, but in the integrated assessment of retinal microcirculation and choroidal structural parameters within a treatment-naïve unilateral neovascular AMD cohort using an intra-individual comparison approach. This design enabled assessment of localized disease-associated alterations while reducing confounding related to age, systemic vascular status, and inter-subject variability.

Abbreviations

AE	Affected eye
AMD	Age-related macular degeneration
BCVA	Best-corrected visual acuity
CC	Cortical cataract
CNV	Choroidal neovascularization
CONAN	Consensus on Neovascular AMD Nomenclature
CVI	Choroidal vascularity index
DCP	Deep capillary plexus
EDI	Enhanced depth imaging
FAZ	Foveal avascular zone
FE	Fellow eye
HEYEX	Heidelberg Eye Explorer
ILM	Internal limiting membrane
IPL	Inner plexiform layer
IRF	Intraretinal fluid
LA	Luminal area
logMAR	Logarithm of the minimum angle of resolution
MNV	Macular neovascularization
nAMD	Neovascular age-related macular degeneration
NS	Nuclear sclerosis
OCT	Optical coherence tomography
OCTA	Optical coherence tomography angiography
OPL	Outer plexiform layer
PD	Perfusion density
PED	Pigment epithelial detachment
PCIOL	Posterior chamber intraocular lens

PSCC	Posterior sub capsular cataract
RPE	Retinal pigment epithelium
ROI	Region of interest
SCP	Superficial capillary plexus
SFCT	Subfoveal choroidal thickness
SRF	Subretinal fluid
SSI	Signal strength index
TCA	Total choroidal area
VD	Vessel density
VEGF	Vascular endothelial growth factor

Author contributions

Conceptualization: SR, KS, PB; Methodology: SR, KS, PB, LS, SS, RA; Data collection: SR Imaging analysis: SR, KS, PB; Statistical analysis and result interpretation: SR, KS, PB Original draft preparation: SR Manuscript review and editing: SR, KS, PB, LS, SS, RA. All authors have read and agreed to the final version of the manuscript. Acknowledgements: NA.

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Data availability

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

Declarations

Ethics approval and consent to participate

This study adhered to the tenant of the declaration of Helsinki and was approved by the institutional review committee of National Academy of Medical Sciences, Bir Hospital with ethical reference number 33/2082/83.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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