Peripapillary Perfused Capillary Density in Exfoliation Syndrome and Exfoliation Glaucoma versus POAG and Healthy Controls: An OCTA Study

Yanin Suwan, MD,† Lawrence S. Geyman, MD,*‡ Masoud Aghsaei Fard, MD,§ Apichat Tantraworasin, MD, PhD,¶ Toco Y. Chui, PhD,* Richard B. Rosen, MD,* and Robert Ritch, MD**

Purpose: To compare the peripapillary perfused capillary density (PCD) among eyes with exfoliation syndrome (XFS), exfoliation glaucoma (XFG), primary open-angle glaucoma (POAG), and controls.

Design: Observational, cross-sectional study.

Methods: Optical coherence tomography angiography (OCTA) images (4.5 × 4.5 mm) of the optic nerve head were obtained using a commercial spectral domain OCTA system (AngioVue Avanti RTVue-XR, OptoVue, Fremont, CA). Two concentric circles with 1.95-mm (inner) and 3.45-mm (outer) diameters were placed manually, producing an annulus of width 0.75 mm centered at the optic disc. PCD was calculated as the ratio of pixels associated with capillaries to the pixels in the annulus after large blood vessel removal. Continuous variables were assessed by analysis of variance and Tukey honest significant difference (HSD) test. Multiple linear regression analysis was performed to adjust for confounding factors.

Results: Forty-three XFG eyes, 31 POAG eyes matched for visual field mean deviation, 33 XFS eyes, and 45 control eyes were analyzed. PCD demonstrated a progressive decrease from controls to XFS to POAG to XFG. Pairwise comparisons revealed significant differences in PCD between each pair of groups (all $P < 0.01$) except for PCD between XFS and POAG ($P = 0.08$). A multivariable model adjusting for age and stage showed a more significant decrease in PCD in XFG compared with POAG ($P = 0.001$).

Conclusions: PCD was more significantly decreased in XFG compared with POAG eyes and in XFS compared with control eyes. OCTA provides the first quantitative evidence of the microvascular disturbance that accompanies XFS.

Key Words: optical coherence tomography angiography, exfoliation syndrome, exfoliation glaucoma, glaucoma, vessel density

(Asia-Pac J Ophthalmol 2017;6:0–0)

From the *Eihorn Clinical Research Center, New York Eye and Ear Infirmary of Mount Sinai, New York, NY; †Ramathibodi Hospital, Mahidol University, Bangkok, Thailand; ‡Icahn School Medicine at Mount Sinai, New York, NY; §Farabi Eye Hospital, Tehran, Iran; and ¶Department of Surgery, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand.

Received for publication July 14, 2017; accepted October 4, 2017.

Presented in part at the Association for Research in Vision and Ophthalmology Annual Meeting from May 7–11, 2017.

Supported in part by The Matthew and Lee Sabatine Research Fund of the New York Glaucoma Research Institute, New York, NY; Marrus Family Foundation, Bendheim-Lowenstein Family Foundation; Wise Family Foundation, New York Eye and Ear Infirmary Chairman's Research Fund; Violett Fund; and Milbank Foundation. The sponsors or funding organizations had no role in the design or conduct of this research.

R.B.R. is a consultant for Carl Zeiss Meditech and OptoVue.

Y.S. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

The authors have no other funding or conflicts of interest to declare.

Reprints: Yanin Suwan, MD, Department of Ophthalmology, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand. E-mail: yanin.suwan@gmail.com.

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ISSN: 2162-0989

DOI: 10.22608/APO.2017318

Exfoliation syndrome (XFS) is the most common identifiable cause of open-angle glaucoma worldwide.[1] Exfoliation syndrome is also associated with an iris vasculopathy marked by degeneration of the smooth muscle cells, pericytes, and endothelial cells; abnormalities of the endothelial basement membrane; and obliteration of the lumen.[2–4] In addition, the vascular dysregulation beyond normal age-related decline may also play a role both in the development and worsening of the systemic cardiovascular diseases in XFS.[5] Systemic cardiovascular associations include transient ischemic attacks, hypertension, angina, myocardial infarction, cerebrovascular and cardiovascular disease, and aortic aneurysm.[6] Although increased intraocular pressure (IOP) is considered to be the only modifiable risk factor proven to delay glaucoma progression, there is increasing evidence that the pathogenesis of glaucoma is also linked to disturbed ocular blood flow (OBF).[7–9] Indeed, impaired retrobulbar hemodynamics have been identified using color Doppler imaging and laser Doppler flowmetry in XFS and exfoliation glaucoma (XFG).[10–13]

Optical coherence tomography angiography (OCTA) is a new noninvasive imaging technique that employs en face reconstruction of OCT combined with motion contrast processing to reveal perfused retinal vasculature.[14] Split-spectrum amplitude decorrelation angiography (SSADA), a novel OCTA algorithm, compares the decorrelation signal between sequential OCT B-scans taken at precisely the same cross-section to construct a map of blood flow. Prior studies using OCTA reported a decrease in the peripapillary vessel density in eyes with primary open-angle glaucoma (POAG) compared with controls.[14–18] However, it is not known if differences exist in peripapillary vessel density among XFS, XFG, POAG, and control eyes. As previous studies reported decreased blood flow in exfoliation syndrome and exfoliation glaucoma, we hypothesized that differences in peripapillary vessel density exist among the 4 groups. The aim of this study was to compare peripapillary perfused capillary density (PCD) with OCTA among these 4 groups.

MATERIALS AND METHODS

Participants

This cross-sectional study was approved by the New York Eye and Ear Infirmary of Mount Sinai Institutional Review Board. Written, informed consent was obtained from all subjects and the study adhered to the Health Insurance Portability and Accountability Act and the tenets of the Declaration of Helsinki.

Exfoliation syndrome was defined as the presence of exfoliation material on clinical examination, a normal appearing optic nerve, and the lack of glaucomatous damage on OCT and perimetry.

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Exfoliation glaucoma was defined as XFS with a glaucomatous-appearing optic nerve (neuroretinal rim thinning or notching), retinal nerve fiber layer (RNFL) thinning on OCT outside the 95% confidence interval (CI) of the normal distribution, and a visual field defect on 24-2 Swedish Interactive Thresholding Algorithm (SITA) standard perimetry as defined in the following paragraph.

Primary open-angle glaucoma was defined as a glaucomatous-appearing optic nerve (neuroretinal rim thinning or notching), RNFL thinning on OCT outside the 95% confidence interval of the normal distribution, and a visual field defect on 24-2 SITA standard perimetry. A visual field (VF) defect was defined as 3 contiguous points at a 5% level of significance on the pattern deviation plot with 1 of the 3 points at a 1% level of significance, or a glaucoma hemifield test outside normal limits, or a pattern standard deviation (PSD) outside normal limits ($P < 0.05$), consistent with a glaucomatous pattern. The VF results were considered reliable at values of fixation loss of 15% or less, false-positive rate of 15% or less, and false-negative rate of 15% or less. In classifying POAG subjects by stage, mild was defined as mean deviation (MD) greater than −6 dB, moderate as −6 to −12 dB, and severe as less than −12 dB.

Control eyes were defined as follows: no evidence of retinal pathology or glaucoma, IOP of 21 mm Hg or less, no chronic ocular or systemic corticosteroid use, an open anterior chamber angle on gonioscopy, absence of exfoliation material, normal-appearing optic discs, retinal nerve fiber layer thickness (RNFLT) measured on OCT within the 95% confidence interval of the normal distribution, and no visual field defects on 24-2 SITA standard tests as defined above. All patients had best-corrected visual acuity (BCVA) of at least 20/40 and were 20 years of age or older.

Exclusion criteria for all eyes included a history of ocular surgery apart from uncomplicated cataract surgery, vitreoretinal diseases or nonglaucomatous optic neuropathy, diabetes mellitus, and cardiovascular disease other than treated systemic hypertension. One eye from each participant was enrolled. In patients with unilateral XFS or XFG, affected eyes were imaged and analyzed. In cases where both eyes of a glaucoma patient or a normal subject met the inclusion criteria, only the right eye was selected for the study.

All glaucoma patients underwent a comprehensive ophthalmic examination, including measurements of BCVA (Snellen), slit-lamp biomicroscopy, IOP measurement using Goldmann applanation tonometry, and dilated fundus examination using a 78-diopter (D) lens. Visual field examinations were performed on the Humphrey Visual Field Analyzer (Humphrey Instruments Model Model 740; Carl Zeiss Meditec, Dublin, CA) using the 24-2 SITA standard program.

Optical coherence tomography RNFLT analysis (Spectralis OCT Version 6.0.11.0 + Glaucoma Module Premium Edition Software; Heidelberg Engineering, GmbH, Dossenheim, Germany) was performed before OCTA. A circle scan 3.45 mm in diameter centered over the optic nerve head was then taken to yield average circumpapillary RNFLT (cpRNFLT) values. Average RNFLT was used for comparison with OCTA data. Scans with signal strength less than 7/10 were excluded.

Optical Coherence Tomography Angiography

In this study, OCTA images were obtained with a commercial spectral domain OCT system (AngioVue Software Version 2015.100.0.35, Optovue, Fremont, CA). Each patient underwent a single imaging session consisting of 2 volumetric raster scans (1 vertical and 1 horizontal) centered on the optic nerve head and covering an area 4.5 × 4.5 mm. Each raster scan consisted of 304 B-scans, which were each scanned twice for a total 608 B-scans. Each B-scan consisted of 304 A-scans. With an A-scan rate of 70,000 A-scans per second, each raster scan took less than 3 seconds.

To produce images of perfused vessels, the SSADA algorithm was employed.[17,19] Additional software segmented the cross-sectional OCT retinal image into distinct layers. To sample the radial peripapillary capillary (RPC) vasculature, we analyzed the vessels located between the internal limiting membrane (ILM) and the posterior boundary of the RNFL. Images of signal strength index less than or equal to 40 and those with eye motion artifacts were excluded.[20]

OCTA Image Analysis

The OCTA images were analyzed using a custom MATLAB program as described previously (The Mathworks, Inc, Natick, MA).[14,18] After the removal of large blood vessels, local adaptive thresholding was performed using a sampling window size of 15 × 15 pixels to account for local differences in brightness throughout the image.

Annular and Sectoral PCD (%)

To calculate annular and sectoral PCD, an outer circle 3.45 mm in diameter was placed concentric to the inner 1.95-mm circle, producing an annular region of interest (ROI) with a width of 0.75 mm. This 3.45-mm outer circle diameter parallels the dimensions of the standard cpRNFLT circle scan currently employed in the majority of commercially available OCT systems. To ensure that the same ROI was included in all OCTA images, PCD within a fixed annular ROI was extracted for quantitative analysis. Then, PCD was calculated as a percentage by dividing the area associated with perfused capillaries (white pixels) over the area of the ROI in question (either the entire annulus or 1 of the four 90-degree sectors). A color-coded PCD map was generated by computing the PCD within a 16 × 16-pixel sampling window with 8-pixel overlaps over the binary image.

Global Perfused Capillary Density (%)

Global PCD was calculated by generating a percentage of the number of pixels associated with perfused capillaries over the number of pixels in the entire image after removal of the inner 1.95-mm circular area and the large blood vessels.

Statistical Analysis

One eye per subject was selected for analysis. The distribution of numerical data was tested for normality using the Shapiro-Wilk test. Descriptive statistics were calculated as the mean and standard deviation for normally distributed variables. Categorical variables were compared using the Fisher exact test. Continuous variables were compared using an analysis of variance (ANOVA) and a pairwise Tukey-Kramer honest significant difference. Multiple linear regression adjusted for age, stage, and axial length was used to identify the effect of types of glaucoma on PCD (XFG vs POAG).

Diagnostic accuracy for differentiating between (1) control and XFS eyes and (2) XFG and POAG eyes was evaluated by

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TABLE 1. Clinical and Demographic Characteristics

	Control n = 45	XFS n = 33	XFG n = 43	POAG n = 31	*P*
Age, y*	58.4 ± 10.2	69.0 ± 13.1	71.2 ± 10.1	60.7 ± 8.5	<0.001†
Sex, female (%)	30 (66.7)	17 (51.5)	22 (58.1)	17 (53.1)	0.522‡
Axial length, mm*	22.9 ± 1.3	23.2 ± 1.2	23.9 ± 1.6	23.7 ± 0.9	0.019†
Glaucoma severity, mild:moderate:severe	NA	NA	25:10:8	15:8:8	0.703‡
Visual field MD, dB*	−0.6 ± 1.3	−0.8 ± 1.9	−7.4 ± 6.8	−9.3 ± 9.4	<0.001†
Visual field PSD, dB*	1.3 ± 1.0	1.3 ± 1.2	5.8 ± 3.7	6.0 ± 3.9	<0.001†
RNFLT, μm*	98.5 ± 9.4	94.1 ± 14.1	72.8 ± 15.0	70.1 ± 15.1	<0.001†
PCD, %					
Global*	42.4 ± 2.2	38.0 ± 3.8	29.4 ± 7.5	34.4 ± 6.6	<0.001†
Annular*	43.9 ± 2.1	39.6 ± 3.9	30.7 ± 8.1	36.2 ± 7.0	<0.001†
Superior*	43.9 ± 2.1	38.9 ± 4.6	28.8 ± 9.6	34.4 ± 9.1	<0.001†
Nasal*	43.3 ± 3.0	38.6 ± 5.3	29.3 ± 8.7	39.2 ± 5.8	<0.001†
Inferior PCD, %*	43.6 ± 2.2	39.1 ± 5.4	29.9 ± 9.4	36.8 ± 8.5	<0.001†
Temporal PCD, %*	44.8 ± 2.1	41.9 ± 2.6	34.8 ± 8.5	34.2 ± 8.5	<0.001†

NA indicates not available.

*Baseline clinical data reported as mean ± standard deviation.

†*P* value among 4 groups (1-way ANOVA).

‡*P* value between XFG and POAG (χ^2 test).

calculating the area under the receiver operating characteristic (AUROC) curves. The AUROC curves were adjusted for age differences between groups using a covariate adjustment regression method. Pairwise comparisons of the AUROCs were performed to evaluate whether there were statistically significant differences between AUROC values. All statistical analyses were performed with Stata version 14 (StataCorp LP, College Station, TX). The alpha level (type I error) was set at 0.05 for all comparisons.

RESULTS

Study Population

Initially, 33 eyes with XFS, 44 eyes with XFG, 31 eyes with POAG, and 45 controls met the inclusion criteria for this study. Among the eyes, 1 XFG eye was excluded because of the unacceptable OCTA image quality. There were significant differences among the 4 groups in terms of age, axial length, RNFLT, and visual field mean deviation and pattern standard deviation ($P < 0.01$; Table 1). There was an equal distribution of mild, moderate, and severe glaucoma patients in the XFG and POAG groups ($P = 0.70$). There was no significant difference in mean VF MD, VF PSD, and average RNFLT between XFS versus controls and between XFG versus POAG (Table 2).

TABLE 2. Comparisons Between Control vs XFS and XFG vs POAG

	Mean Difference	95% CI
Control vs XFS		
MD	0.032	−0.797, 0.861
PSD	−0.013	−0.578, 0.551
RNFLT	−2.143	−8.366, 4.079
XFG vs POAG		
MD	−1.232	−5.561, 3.098
PSD	−0.922	−2.951, 1.108
RNFLT	−1.032	−9.396, 7.333

PCD Analysis

Global, annular, and all 4 sectoral PCDs demonstrated a significant difference in PCD among the 4 groups (all $P < 0.001$; Table 1; Fig. 1). Pairwise comparisons revealed significant differences in both annular and global PCD between each group [all $P < 0.05$ except for annular PCD in XFS vs POAG ($P = 0.08$), Table 3]. A multiple linear regression analysis adjusted for age, stage, and axial length showed a decrease in annular PCD between controls versus XFS with percent difference of 3.8% (95% CI, −5.3 to −2.2) and XFG versus POAG with percent difference of 7.1% (95% CI, 4.3 to 9.8). There were similar findings of differences in global PCD between controls versus XFS with percent difference of −4.0% (95% CI, −5.6 to −2.4) and XFG versus POAG with percent difference of 6.1% (95% CI, 3.5 to 8.7).

Diagnostic Capability Analysis

Diagnostic accuracy for differentiating between (1) control and XFS eyes and (2) XFG and POAG eyes was evaluated by calculating the AUROC curves shown in Figure 2. No significant difference was found in the AUROC based on annular and global PCD ($P = 0.78$ and 0.87 for control vs XFS and XFG vs POAG, respectively).

DISCUSSION

To our knowledge, this is the first study to compare PCD among XFS, XFG, POAG, and controls using OCTA. Overall, we found a progressive decrease in PCD from controls to XFS to POAG to XFG ($P < 0.001$).

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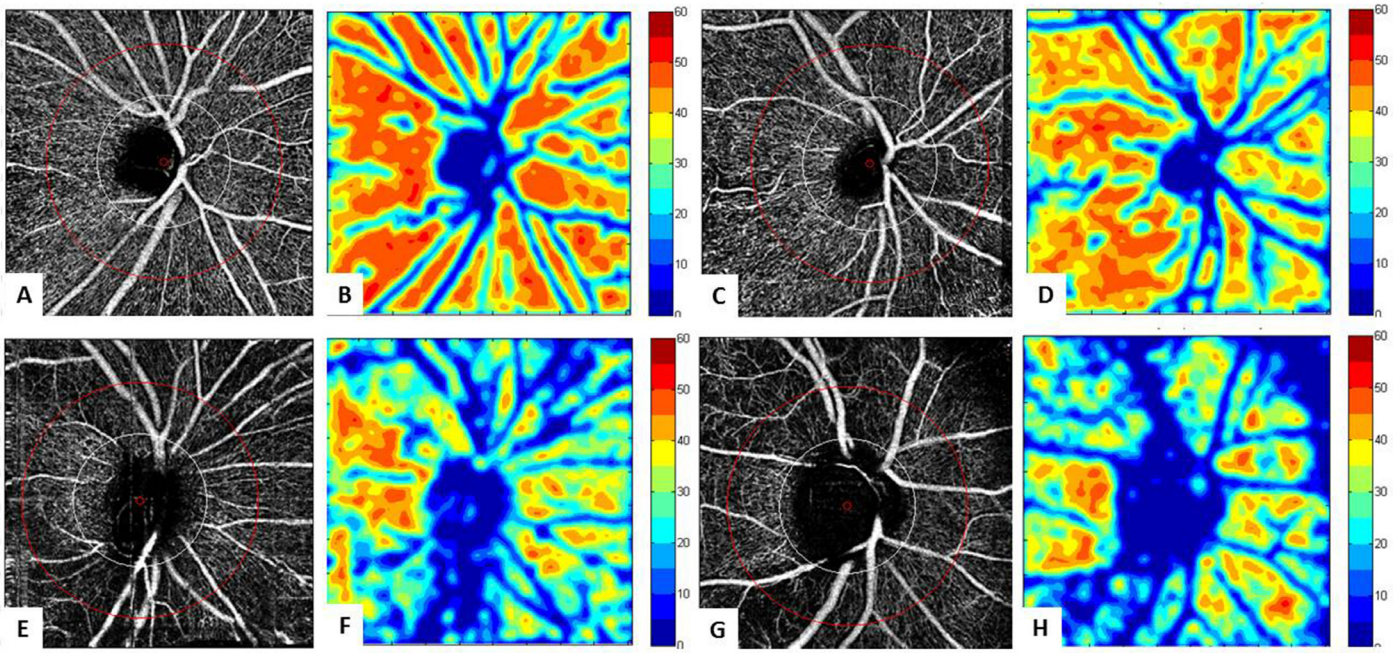

FIGURE 1. OCTA images in gray scale (left of each pair) and color perfused capillary density map (right). A–B, Control; C–D, exfoliation syndrome; E–F, primary open-angle glaucoma; G–H, exfoliation glaucoma.

Exfoliation syndrome has been linked to both intraocular and extraocular vascular pathology, including anterior segment ischemia, retinal vein occlusion, and cerebrovascular and cardiovascular disease.[21,22] Exfoliation material accumulating pericellularly may disrupt the normal basement membrane of the cells, causing degenerative fibrillopathy and impaired endothelial function.[23,24] Increased oxidative stress and decreased antioxidant protection probably play a role in the development and progression of vessel wall damage and systemic vascular dysregulation.[5] The vasoactive peptide endothelin-1 is significantly increased in the aqueous of XFS patients, whereas levels of nitric oxide were decreased in XFS patients resulting in obliterative vasculopathy and causing local ischemia.[6,25,26] Exfoliation syndrome has been known to be associated with ocular ischemia, anterior segment hypoxia, and reduced ocular and retrobulbar blood flow.[6,11,27] Yuksel et al[11] reported decreased end diastolic velocities in short posterior ciliary arteries compared with controls. Exfoliation syndrome is also associated with thin RNFLT compared with healthy age-matched controls.[28,29] We demonstrated a decreased PCD in XFS compared with controls, suggesting that microvascular attenuation accompanies RNFL thinning and may precede visual field losses.

Although both POAG and XFG eyes demonstrated decreased PCD values compared with controls, XFG eyes demonstrated lower PCD values compared with POAG eyes after adjusting for age and stage. This finding corroborates the present understanding of XFG as a particularly aggressive type of open-angle glaucoma, which often progresses at a more rapid rate and responds more poorly to medical therapy compared with POAG. Similarly, prior studies reported an increased vascular resistance in the ophthalmic artery in exfoliation glaucoma.[13] Such resistance may be due to the increased vascular rigidity secondary to the accumulation of exfoliation material in the walls of the retrobulbar blood vessels.[30]

We recruited a wide range of phakic refractive error eyes

TABLE 3. Post Hoc Comparisons of Annular PCD Using Tukey HSD

	Control	XFS	XFG	POAG
Annular PCD				
Control	1	0.008*	<0.001*	<0.001*
XFS		1	<0.001*	0.080
XFG			1	0.001*
POAG				1
Global PCD				
Control	1	0.003*	<0.001*	<0.001*
XFS		1	<0.001*	0.045*
XFG			1	0.001*
POAG				1

HSD indicates honest significant difference.

*Mean difference is significant at the 0.05 level.

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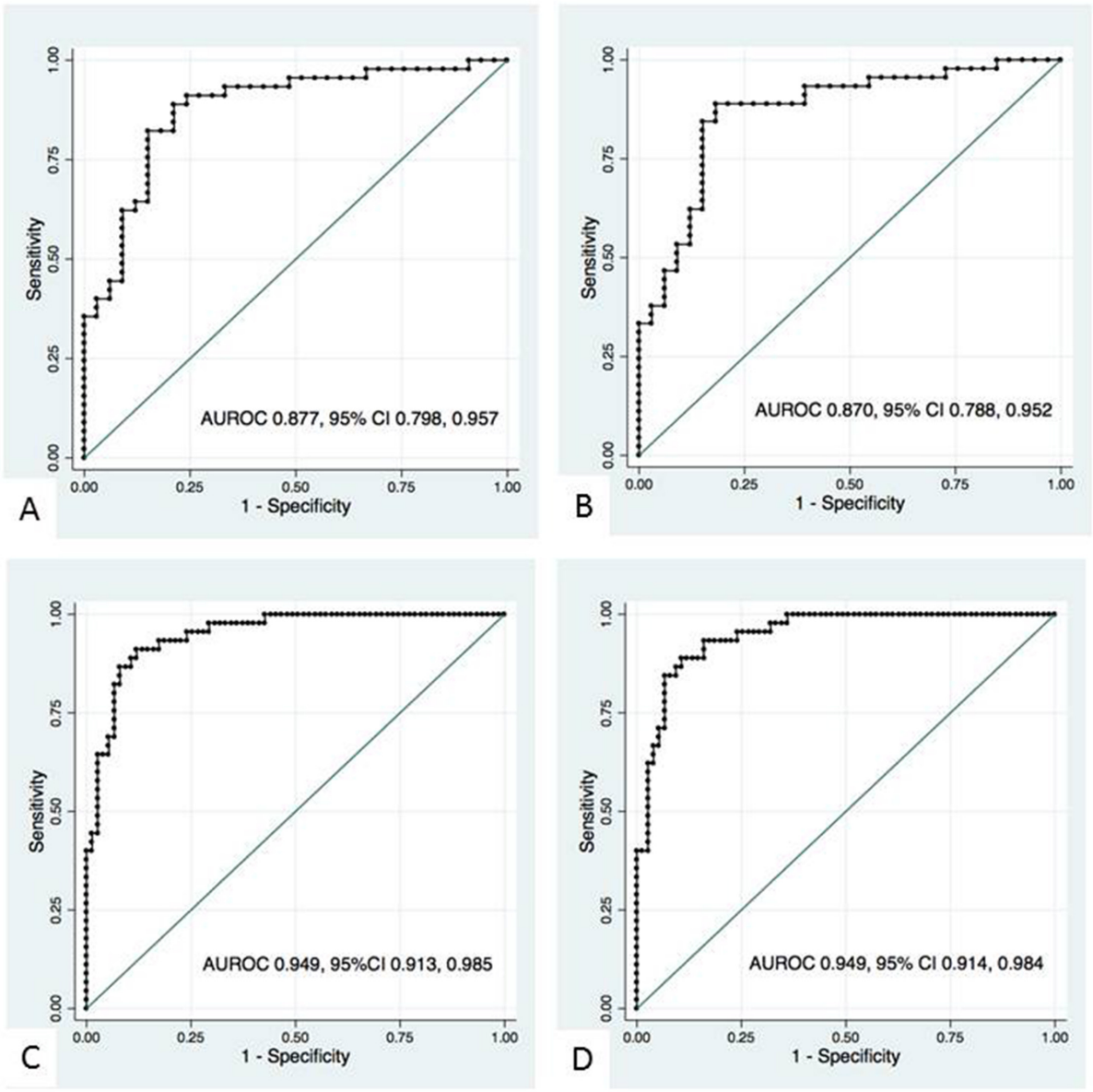

FIGURE 2. AUROC depicting the capability of PCD to distinguish between the following: A, annular PCD between controls versus XFS; B, global PCD between controls versus XFS; C, annular PCD between XFG versus POAG; D, global PCD between XFG versus POAG.

in our study. In high myopia, segmentation error from peripapillary atrophy and posterior staphyloma commonly occurs and is unavoidable. To exclude the influence of such artifact, we only analyzed eyes with segmentation errors located outside the ROI. With myopic progression, axial elongation stretches the retina and may lead to a decrease in the retinal microvascular density.[31,32] In contrast, a decrease in microvascular density may be caused by reduced blood supply demands due to the retinal thinning and degeneration in myopia. After adjusting for the effect of axial length on PCD using multiple linear regression, the differences between groups still persist.

There are a number of limitations to our study. First, the relatively small sample size and cross-sectional nature of the study limited the power of our findings. Second, we have included a relatively high proportion of older age patients in the XFS and XFG groups, as both are age-related diseases.[33–39] Because advanced age could affect the microvasculature around the optic disc, we sought to eliminate the effect of age on PCD through multiple linear regression analysis. Third, due to the cross-sectional nature of this study, patients were not followed over time, and as such, we could not determine disease progression.

In summary, this study provided the first quantitative evidence of the microvascular disturbance accompanying XFS. However, the causality between decreased PCD and glaucomatous damage in exfoliation syndrome and glaucoma remains to be determined. Future research is necessary to determine the roles of OCTA as a diagnostic parameter for detecting exfoliation syndrome, predicting the risk of glaucoma development, and assessing glaucomatous progression and retinal blood flow in patients with progressive and stable XFG.

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