The Role of Optical Coherence Tomography Angiography in Moderate and Advanced Primary Open-Angle Glaucoma

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Research Article

Keywords: Primary open-angle glaucoma, Optical coherence tomography angiography, Structure-function correlation, Vasculature-function correlation

Posted Date: July 19th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-710633/v1>

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Abstract

Purpose: To evaluate the relationship between structure and function in moderate and advanced primary open-angle glaucoma (POAG) and to determine the accuracy of structure and vasculature for discriminating moderate from advanced POAG.

Methods: In this cross-sectional study 25 eyes with moderate and 40 eyes with advanced POAG were enrolled. All eyes underwent measurement of the thickness of circumpapillary retinal nerve fiber layer (cpRNFL) and macular ganglion cell complex (GCC), and optical coherence tomography angiography (OCTA) of the optic nerve head (ONH) and macula. Visual field (VF) was evaluated by Swedish interactive threshold algorithm and 24-2 and 10-2 patterns. The correlation between structure and vasculature and the mean deviation (MD) of the VFs was evaluated by a partial correlation coefficient. The area under the receiver operating characteristic curve (AUC) was applied for assessing the power of variables for discrimination moderate from advanced POAG.

Results: Superior cpRNFL, superior GCC, whole image vessel density (wiVD) of the ONH area, and vessel density in inferior quadrant of perifovea had the strongest correlation with the mean deviation (MD) of the VF 24-2 ($r = .351, .558, .649$ and $.397$; $p < .05$). The greatest AUCs belonged to inferior cpRNFL (.789), superior GCC (.818), vessel density of the inferior hemifield of ONH area (.886), and vessel density in inferior quadrant of perifovea (.833) without statistically significant difference in pairwise comparison.

Conclusion: Vasculature has a stronger correlation than the structure with MD in moderate and advanced POAG and is as accurate as structure in discrimination moderate from advanced POAG.

Introduction

Glaucomatous optic neuropathy as the sine qua non of glaucoma will result due to the damage to retinal ganglion cells (RGCs). Continuous and progressive damage to the axons of RGCs will lead to characteristic optic nerve head (ONH) appearance and visual field defects [1]. In addition to intraocular pressure (IOP) which is the main risk factor for the development and progression of glaucoma, impaired blood flow to the ONH may have a role in the pathophysiology of the disease [2–4].

Quantitative measurements of the thickness of the circumpapillary retinal nerve fiber layer (cpRNFL) and inner macular layers are provided by spectral-domain optical coherence tomography (SD-OCT) [5]. Because of a “floor effect” in the thickness of the cpRNFL in the advanced stages of glaucoma, following the patients with visual fields is a better indicator of progression and establishes a practical mean for adjusting the treatment [6–9]. The thickness of the inner macular layers is less likely to be suffered from such effect and is useful even in the advanced stages of glaucoma [10, 11].

In recent years non-invasive qualitative and quantitative imaging of ocular blood flow has been provided by optical coherence tomography angiography (OCTA) [12]. Vessel density (VD) measurements by OCTA in the circumpapillary and macular area are repeatable and reproducible and are affected in different

stages of glaucoma to various extents [4, 13, 14]. Comparing to OCT, OCTA reaches the floor in more advanced stages of glaucoma [15]. Albeit, macular VD may not have a detectable floor and be useful for monitoring the progression in the advanced stage [16].

Given the advantages of OCTA in later stages of the glaucoma continuum when OCT reaches the floor, the current investigation aimed to evaluate the correlation between different structural parameters and visual field sensitivity. Determination of the accuracy of VD in different areas for the detection of severe glaucoma was another purpose of the study.

Methods

Eyes suffering from moderate and advanced primary open-angle glaucoma (POAG) were recruited to this cross-sectional study. The ethics committee of Tehran University of Medical Sciences approved the study protocol and the tenets of the declaration of Helsinki have adhered. All patients signed the informed consent form.

All patients underwent a thorough and comprehensive ophthalmic examination including corrected distance visual acuity (CDVA), slit-lamp biomicroscopy, measurement of IOP by Goldmann applanation tonometry, pachymetry, and funduscopy. Evaluation of the visual field (VF) by the Swedish Interactive Thresholding Algorithm (SITA) standard strategy and 24 – 2 and 10 – 2 patterns was done for each patient (Humphrey Field Analyzer, Carl Zeiss Meditec, Fremont, CA).

65 eyes of 45 patients having primary open-angle glaucoma (POAG) were included in the current investigation. To be included in the study the following criteria should be satisfied:

1. Age over 18 years.
2. Spherical and astigmatic refractive error in the range of ± 5 and ± 3 diopters of sphere and cylinder, respectively.
3. Mean deviation (MD) worse than -6.00 in the VF 24 – 2 by SITA standard strategy.

Eyes with a history of intraocular surgery other than uncomplicated cataract and glaucoma surgery, diabetic retinopathy, age-related macular degeneration, retinal vascular disorders, and trauma were excluded.

POAG was defined as the presence of an open-angle in gonioscopy, glaucomatous optic neuropathy (e.g., generalized enlargement of the cup, notching of the neuroretinal rim), or thinning of the cpRNFL evidenced by SD-OCT and associated VF defects without secondary causes.

All patients were under standard care at the glaucoma clinic of Farabi Eye Hospital and were familiar with perimetry. Evaluation of the central 10 and 24 degrees of VF was done by SITA standard strategy and HFA II for each patient on the same day. A 2-hour gap was considered for resting between perimetries. Glaucomatous damage of VF was defined as the presence of a glaucoma hemifield test outside normal

limits or a pattern standard deviation (PSD) with a P less than 5% on two reliable (Fixation loss < 25% and False positive < 15%) consecutive VFs. The last VF was included in the analysis.

Spectral-Domain Optical Coherence Tomography

All eyes underwent cpRNFL and macular scan by RTVue-100 SD-OCT (Optovue, Inc., Fremont, CA, USA). Topical tropicamide 0.5% was used for dilation of the pupil before imaging. This device measures the thickness of the cpRNFL on a 3.45 mm diameter circle. The thickness of cpRNFL as average (average cpRNFL), inferior, and superior hemifield and in the superotemporal (ST), temporal upper (TU), temporal lower (TL), inferotemporal (IT), inferonasal (IN), nasal lower (NL), nasal upper (NU), and superonasal (SN) sectors and temporal, inferior, nasal and superior quadrants were included in the analysis.

RTVue measures the thickness of macular RNFL, ganglion cell, and inner plexiform layers (IPL) as ganglion cell complex (GCC) which are representative of axons, cell bodies, and dendrites of RGCs, respectively. A 7*7 mm² area was used to measure the thickness of GCC 1 mm temporal to the fovea. The thickness of average, superior, and inferior GCC are provided in the printout. Global loss volume (GLV) and focal loss volume (FLV) which represent the global and focal loss of GCC in the entire GCC map are also available. Only images with a signal strength index (SSI) of more than 40 were included in the analysis.

Optical Coherence Tomography Angiography

Three-dimensional OCTA of the ONH and macula (RTVue XR Avanti, Optovue Inc., Fremont, CA, USA) with the AngioVue OCT Angiography software (software 2.0.5.39, Optovue, Inc., Fremont, CA, USA) was done for all the study eyes after proper dilation of the pupil with tropicamide 0.5% and between 9 a.m. and 11 a.m. The software calculates the area occupied by actively flowing vessels as percentages by the split-spectrum amplitude-decorrelation angiography (SSADA) algorithm [12]. Pixels that have a decorrelation value above the threshold will be recognized as blood flow in this algorithm.

The OCTA of the ONH was done in a 4.5*4.5 mm² area with the center of the optic disc.

Vessel density (VD) and capillary density (CD) with automated removal of the large vessels was measured in the radial peripapillary slab (RPC) between the internal limiting membrane (ILM) and posterior border of RNFL [17]. Parameters included in the analysis were whole image VD (wiVD), inside disc VD (idVD), circumpapillary VD (cpVD), superior hemi VD (shVD), inferior hemi VD (ihVD), whole image CD (wiCD), inside disc CP (idCD), circumpapillary CD (cpCD), superior hemi CD (shCD) and inferior hemi CD (ihCD).

Vessel density in the slabs of the superficial capillary plexus (SCP) and deep capillary plexus (DCP) was measured by a 6*6 mm² volumetric macular scan in the parafoveal and perifoveal region. Capillaries between ILM and posterior boundary of the IPL and capillaries between the posterior boundary of the IPL and posterior boundary of the outer plexiform layer (OPL) conform SCP and DCP, respectively [18]. The

parafoveal region refers to an annulus centered on the fovea with an inner radius of 1 mm and an outer radius of 3 mm. The annulus surrounding the parafoveal region with the same center and outer radius of 6 mm forms the perifoveal region. Whole image vessel density (wiVD), superior hemi vessel density (shVD), inferior hemi vessel density (ihVD), whole ETDRS vessel density (wETDRSVD), Foveal vessel density (fVD), parafoveal vessel density (parafVD), parafoveal superior hemi vessel density (parafshVD), parafoveal inferior hemi vessel density (parafihVD), parafoveal vessel density in the inferior quadrant (parafiVD), parafoveal vessel density in the superior quadrant (parafsVD), parafoveal vessel density in the nasal quadrant (parafnVD), parafoveal vessel density in the temporal quadrant (paraftVD), perifoveal vessel density (perifVD), perifoveal superior hemi vessel density (perifshVD), perifoveal inferior hemi vessel density (perifihVD), perifoveal vessel density in the inferior quadrant (perifiVD), perifoveal vessel density in the superior quadrant (perifsVD), perifoveal vessel density in the nasal quadrant (perifnVD) and perifoveal vessel density in the temporal quadrant (paraftVD) in the SCP were included in the analysis.

Statistical Analyses

To present data we used mean, standard deviation, median, and range. To compare the groups considering the probable correlation of the measurements in the eyes, we used GEE (Generalized Estimating Equation) models. To assess the predictive ability of variables to detect the severity of glaucoma we used the receiver operating characteristic (ROC) curve and area under the ROC curve (AUC). To detect a significant difference between AUCs, a pairwise comparison was performed. To obtain the relation of the variables, while considering the dependency of the eyes, we used a partial correlation coefficient. All statistical analysis was performed by SPSS (version 26.0). A P-value less than 0.05 considered statistically significant.

Results

Twenty-five eyes with moderate and 40 eyes with advanced glaucoma were enrolled in the current investigation. The mean age for the entire group was 56.53 ± 18.99 years and 16 (35.6%) patients were female. Baseline clinical and demographic data are shown in Table 1. Corrected distance visual acuity wasn't different between eyes with moderate and advanced glaucoma ($.25 \pm .24$ versus $.29 \pm .18$; $p = .305$). Eyes with advanced glaucoma higher vertical cup to disc ratio (VCDR) ($.83 \pm .10$ versus $.89 \pm .13$; $p < .035$).

Table 1
Baseline demographic and clinical data in eyes with moderate and advanced glaucoma.

	Moderate Glaucoma		Severe Glaucoma		P
Age (Years, Mean ± SD)	56.52 ± 16.30		60.22 ± 17.90		.404 [†]
Gender (Male/Female, %)	13/12 (52.0/48.0)		30/10 (75.0/25.0)		.057 [‡]
CDVA (LogMAR, Mean ± SD)	.25 ± .24		.29 ± .18		.305 [¥]
VCDR (Mean ± SD)	.83 ± .10		.89 ± .13		.035 [†]
IOP (mmHg, Mean ± SD)	16.76 ± 7.70		17.07 ± 6.04		.855 [†]
CCT (µm, Mean ± SD)	532.76 ± 34.76		523.35 ± 31.19		.262 [†]
Medications (Number, %)	0	9 (36.0)	0	7 (17.5)	
	1	0 (0.0)	1	7 (17.5)	
	2	5 (20.0)	2	6 (15.0)	
	3	8 (32.0)	3	10 (25.0)	
	4	3 (12.0)	4	10 (25.0)	
†Based on independent-samples T Test.					
‡Based on Pearson Chi-Square Test.					
¥Based on Mann-Whitney U Test.					
CDVA, Corrected Distance Visual Acuity; LogMAR, Logarithm of Minimal Angle of Resolution; VCDR, Vertical Cup to Disc Ratio; IOP, Intraocular Pressure; CCT, Central Corneal Thickness					

A comparison between different structural and functional parameters is presented in Table 2. The eyes with severe glaucoma had worse functional status based on the comparison between MD and PSD in VF 10 – 2 and 24 – 2. Considering structural parameters related to cpRNFL and macula, all factors were lower in eyes suffering from advanced glaucoma except average cpRNFL thickness (47.84 $\pm$ 44.25 versus. 37.57 $\pm$ 36.43; p = .115), cpRNFL thickness in the nasal quadrant (83.91 $\pm$ 25.84 versus. 69.48 $\pm$ 20.01; p = .480), superonasal (94.51 $\pm$ 21.37 versus. 79.07 $\pm$ 21.75; p = .360) nasal upper (84.66 $\pm$ 28.90 versus. 69.94 $\pm$ 21.81; p = .602) and nasal lower sectors (69.60 $\pm$ 14.44 versus. 61.78 $\pm$ 15.39; p = .066).

Table 2
comparison of different structural and functional parameters between moderate and severe glaucoma.

	Moderate Glaucoma	Severe Glaucoma	P
SITA 24 – 2 MD (dB, Mean ± SD)	-8.73 ± 1.74	-21.62 ± 6.19	< .001 [†]
SITA 24 – 2 PSD (dB, Mean ± SD)	7.39 ± 2.13	9.41 ± 2.95	.004 [†]
SITA 10 – 2 MD (dB, Mean ± SD)	-5.81 ± 4.37	-13.88 ± 8.86	< .001 [†]
SITA 10 – 2 PSD (dB, Mean ± SD)	5.02 ± 4.24	7.65 ± 3.81	.012 [†]
Average cpRNFL (µm, Mean ± SD)	47.84 ± 44.25	37.57 ± 36.43	.115 [‡]
Superior cpRNFL (µm, Mean ± SD)	85.18 ± 11.86	70.23 ± 15.34	< .001 [‡]
Inferior cpRNFL (µm, Mean ± SD)	85.51 ± 13.96	68.37 ± 14.48	< .001 [‡]
cpRNFL, Temporal Quadrant (µm, Mean ± SD)	73.48 ± 11.35	62.34 ± 15.18	< .001 [‡]
cpRNFL, Superior Quadrant (µm, Mean ± SD)	84.92 ± 21.57	67.19 ± 23.02	.010 [‡]
cpRNFL, Nasal Quadrant (µm, Mean ± SD)	83.91 ± 25.84	69.48 ± 20.01	.480 [‡]
cpRNFL, Inferior Quadrant (µm, Mean ± SD)	89.73 ± 22.62	71.19 ± 17.64	< .001 [‡]
cpRNFL, Temporal Upper (µm, Mean ± SD)	82.041 ± 17.410	69.02 ± 19.38	.001 [‡]
cpRNFL, Superotemporal (µm, Mean ± SD)	94.63 ± 26.49	71.13 ± 25.26	.002 [‡]
cpRNFL, Superonasal (µm, Mean ± SD)	94.51 ± 21.37	79.07 ± 21.75	.360 [‡]
cpRNFL, Nasal Upper (µm, Mean ± SD)	84.66 ± 28.90	69.94 ± 21.81	.602 [‡]
cpRNFL, Nasal Lower (µm, Mean ± SD)	69.60 ± 14.44	61.78 ± 15.39	.066 [‡]
cpRNFL, Inferonasal (µm, Mean ± SD)	82.57 ± 20.54	65.85 ± 16.42	.001 [‡]
cpRNFL, Inferotemporal (µm, Mean ± SD)	101.70 ± 24.85	80.39 ± 22.46	< .001 [‡]
cpRNFL, Temporal Lower (µm, Mean ± SD)	79.97 ± 22.23	65.37 ± 20.186	.001 [‡]
Average GCC (µm, Mean ± SD)	84.06 ± 9.54	72.80 ± 12.01	< .001 [‡]
GCC, Superior (µm, Mean ± SD)	86.23 ± 10.15	72.31 ± 10.98	< .001 [‡]
GCC, Inferior (µm, Mean ± SD)	81.91 ± 11.85	73.33 ± 14.49	.001 [‡]
GCC, FLV (Mean ± SD)	4.30 ± 3.51	8.11 ± 3.49	< .001 [‡]

		Moderate Glaucoma	Severe Glaucoma	P
GCC, GLV (Mean ± SD)		12.74 ± 7.94	23.40 ± 10.55	< .001 [‡]
ONH	wiVD (% , Mean ± SD)	48.77 ± 4.62	40.23 ± 5.37	< .001 [‡]
	idVD (% , Mean ± SD)	50.11 ± 4.32	46.15 ± 8.42	.105 [‡]
	cpVD (% , Mean ± SD)	52.06 ± 6.29	43.24 ± 7.81	< .001 [‡]
	shVD (% , Mean ± SD)	51.95 ± 5.48	42.07 ± 6.71	< .001 [‡]
	ihVD (% , Mean ± SD)	48.32 ± 4.68	38.74 ± 6.02	< .001 [‡]
	wiCD (% , Mean ± SD)	48.26 ± 12.07	41.49 ± 10.83	.024 [‡]
	idCD (% , Mean ± SD)	44.44 ± 10.34	39.39 ± 9.60	.900 [‡]
	cpCD (% , Mean ± SD)	45.35 ± 10.30	36.55 ± 10.15	.093 [‡]
	shCD (% , Mean ± SD)	48.71 ± 6.06	38.83 ± 8.29	< .001 [‡]
	ihCD (% , Mean ± SD)	48.43 ± 8.31	38.76 ± 7.68	< .001 [‡]
Macula	wiVD (% , Mean ± SD)	50.31 ± 11.29	42.87 ± 9.05	.004 [‡]
	shVD (% , Mean ± SD)	42.32 ± 9.30	37.24 ± 6.77	.383 [‡]
	ihVD (% , Mean ± SD)	42.78 ± 9.19	36.98 ± 7.25	.186 [‡]
	wETDRSVD (% , Mean ± SD)	41.83 ± 9.86	36.79 ± 6.94	.312 [‡]
	fVD (% , Mean ± SD)	30.83 ± 14.35	34.14 ± 60.83	.296 [‡]
	parafVD (% , Mean ± SD)	31.38 ± 16.36	39.56 ± 60.96	.731 [‡]
	parafshVD (% , Mean ± SD)	45.73 ± 6.46	55.44 ± 94.98	.057 [‡]
	parafihVD (% , Mean ± SD)	47.17 ± 8.48	40.36 ± 5.97	.067 [‡]
	paraftVD (% , Mean ± SD)	44.06 ± 10.87	39.68 ± 8.74	.417 [‡]
	parafsVD (% , Mean ± SD)	45.18 ± 12.31	38.62 ± 11.56	.767 [‡]
	parafnVD (% , Mean ± SD)	46.01 ± 8.70	41.17 ± 5.11	.960 [‡]
	parafiVD (% , Mean ± SD)	42.61 ± 10.94	39.08 ± 9.55	.119 [‡]
	perifVD (% , Mean ± SD)	42.15 ± 10.42	36.99 ± 8.60	.061 [‡]

	Moderate Glaucoma	Severe Glaucoma	P
perifshVD (% Mean $\pm$ SD)	42.68 $\pm$ 10.16	37.59 $\pm$ 7.27	.406 [‡]
perifihVD (% Mean $\pm$ SD)	43.41 $\pm$ 9.48	37.49 $\pm$ 8.02	.250 [‡]
PeriftVD (% Mean $\pm$ SD)	40.90 $\pm$ 9.06	35.53 $\pm$ 6.23	.027 [‡]
PerifsVD (% Mean $\pm$ SD)	43.32 $\pm$ 6.63	37.78 $\pm$ 5.65	.001 [‡]
perifnVD (% Mean $\pm$ SD)	54.30 $\pm$ 35.79	44.87 $\pm$ 26.11	.039 [‡]
perifiVD (% Mean $\pm$ SD)	52.64 $\pm$ 32.17	42.24 $\pm$ 24.33	.073 [‡]
<p>†Based on independent-samples T Test.</p> <p>‡Based on generalized estimated equations models.</p> <p>SITA, Swedish Interactive Threshold Algorithm; dB, decibel; MD, Mean Deviation; PSD, Pattern Standard Deviation; cpRNFL, circumpapillary Retinal Nerve Fiber Layer; GCC, Ganglion Cell Complex; FLV, Focal Loss Volume; GLV, Global Loss Volume; ONH, Optic Nerve Head; wiVD, whole image Vessel Density; idVD, inside disc Vessel Density; cpVD, circumpapillary Vessel Density; shVD, superior hemi Vessel Density; ihVD, inferior hemi Vessel Density; wiCD, whole image Capillary Density; idCD, inside disc Capillary Density; cpCD, circumpapillary Capillary Density; shCD, superior hemi Capillary Density; ihCD, inferior hemi Capillary Density; fVD, foveal Vessel Density; parafoVD, parafoveal Vessel Density; parafoshVD, parafoveal superior hemi Vessel Density; parafoihVD, parafoveal inferior hemi Vessel Density; paraftVD, parafoveal temporal Vessel Density; parafoSV, parafoveal superior Vessel Density; parafoNV, parafoveal nasal Vessel Density; parafoiVD, parafoveal inferior Vessel Density; perifVD, perifoveal Vessel Density; perifshVD, perifoveal superior hemi Vessel Density; perifihVD, perifoveal inferior hemi Vessel Density; periftVD, perifoveal temporal Vessel Density; perifsVD, perifoveal superior Vessel Density; perifnVD, perifoveal nasal Vessel Density; perifiVD, parafoveal inferior Vessel Density</p>			

Inside disc vessel (50.11 $\pm$ 4.32 versus. 46.15 $\pm$ 8.42; $p = .105$) and capillary density (44.44 $\pm$ 10.34 versus. 39.39 $\pm$ 9.60; $p = .900$) and cpCD (45.35 $\pm$ 10.30 versus. 36.55 $\pm$ 10.15; $p = .093$) was not different between groups but eyes with advanced glaucomatous damage had lower wiVD, cpVD, shVD, ihVD, wiCD, shCD and ihCD ($p < .001$, $p < .001$, $p < .001$, $p < .001$, $p = .024$, $p < .001$ and $p < .001$, respectively). Whole image vessel density of the macular area, periftVD, perifsVD and perifnVD were significantly lower in advanced glaucoma ($p = .004$, $p = .027$, $p = .001$, $p = .039$, respectively).

Partial correlation controlling for patient, age, gender, SSI, and disc area between circumpapillary structural parameters and MD of the VF 24 – 2 and 10 – 2 is presented in Table3. Superior ($r = .351$; $p = .006$) (Fig. 1) and inferior cpRNFL ($r = .341$; $p = .008$) and RNFL thickness in the nasal upper sector ($r = .333$; $p = .009$) had the strongest correlation with the MD of the VF 24 – 2. Considering the correlation between circumpapillary structural parameters and MD of the VF 10 – 2, only cpRNFL in the nasal quadrant ($r = .316$; $p = .014$) (Fig. 1), and RNFL thickness in the superonasal ($r = .279$; $p = .031$) and nasal upper sectors ($r = .274$; $p = .034$) had significant correlation. Partial correlation controlling for patient, age, gender, and SSI was significant between all macular structural parameters and MD of the VF 24 – 2 and

10 – 2 (Table 3). Average GCC thickness in the superior hemifield (Fig. 1), average GCC, and GLV were the parameters with the strongest correlation with the MD of VF 24 – 2 and 10 – 2 (Table 3).

Table 3
Partial Correlation between functional and structural parameters.

		SITA 24 – 2 MD		SITA 10 – 2 MD	
		r	P	r	P
Average cpRNFL		.119	.364 [†]	– .189	.147 [†]
Superior cpRNFL		.351	.006 [†]	.223	.086 [†]
Inferior cpRNFL		.341	.008 [†]	.215	.099 [†]
cpRNFL, Temporal Quadrant		.199	.127 [†]	.172	.188 [†]
cpRNFL, Superior Quadrant		.312	.015 [†]	.099	.451 [†]
cpRNFL, Nasal Quadrant		.280	.003 [†]	.316	.014 [†]
cpRNFL, Inferior Quadrant		.251	.053 [†]	.022	.867 [†]
cpRNFL, Temporal Upper		.172	.189 [†]	.224	.086 [†]
cpRNFL, Superotemporal		.319	.013 [†]	.107	.416 [†]
cpRNFL, Superonasal		.252	.052 [†]	.279	.031 [†]
cpRNFL, Nasal Upper		.333	.009 [†]	.274	.034 [†]
cpRNFL, Nasal Lower		.225	.084 [†]	.123	.349 [†]
cpRNFL, Inferonasal		.262	.043 [†]	.097	.459 [†]
cpRNFL, Inferotemporal		.215	.099 [†]	.069	.600 [†]
cpRNFL, Temporal Lower		.113	.389 [†]	.210	.108 [†]
Average GCC		.475	< .001 [‡]	.433	< .001 [‡]
GCC, Superior		.558	< .001 [‡]	.472	< .001 [‡]
GCC, Inferior		.326	.010 [‡]	.329	.010 [‡]
GCC, FLV		– .434	< .001 [‡]	– .407	.001 [‡]
GCC, GLV		– .511	< .001 [‡]	– .433	< .001 [‡]
ONH	wiVD	.649	< .001 [†]	.321	.012 [†]
	idVD	.328	.011 [†]	.211	.105 [†]

		SITA 24 – 2 MD		SITA 10 – 2 MD	
	cpVD	.479	< .001 [†]	.445	< .001 [†]
	shVD	.510	< .001 [†]	.382	.003 [†]
	ihVD	.529	< .001 [†]	.335	.009 [†]
	wiCD	.169	.198 [†]	.134	.307 [†]
	idCD	.256	.048 [†]	.211	.106 [†]
	cpCD	.347	.007 [†]	.289	.025 [†]
	shCD	.520	< .001 [†]	.441	< .001 [†]
	ihCD	.314	.015 [†]	.303	.018 [†]
Macula	wiVD	.175	.192 [‡]	.174	.196 [‡]
	shVD	.334	.011 [‡]	.286	.031 [‡]
	ihVD	.346	.008 [‡]	.294	.027 [‡]
	wETDRSVD	.321	.015 [‡]	.250	.061 [‡]
	fVD	.093	.492 [‡]	.319	.016 [‡]
	parafVD	.250	.061 [‡]	– .053	.695 [‡]
	parafshVD	.175	.192 [‡]	.089	.510 [‡]
	parafihVD	.231	.083 [‡]	.155	.250 [‡]
	paraftVD	.296	.026 [‡]	.166	.218 [‡]
	parafsVD	.221	.098 [‡]	.084	.536 [‡]
	parafnVD	.084	.533 [‡]	.149	.267 [‡]
	parafiVD	.046	.737 [‡]	.071	.601 [‡]
	perifVD	.349	.008 [‡]	.184	.170 [‡]
	perifshVD	.361	.006 [‡]	.345	.009 [‡]
	perifihVD	.373	.004 [‡]	.341	.010 [‡]
	PeriftVD	.270	.043 [‡]	.291	.028 [‡]

	SITA 24 – 2 MD		SITA 10 – 2 MD	
PerifsVD	.291	.028 [‡]	.273	.040 [‡]
perifnVD	.348	.008 [‡]	.183	.173 [‡]
perifiVD	.397	.002 [‡]	.429	.001 [‡]
<p>†Based on partial correlation coefficient and controlling for patient, age, gender, signal strength index and disc area.</p> <p>‡ Based on partial correlation coefficient and controlling for patient, age, gender and signal strength index.</p> <p>SITA, Swedish Interactive Threshold Algorithm; MD, Mean Deviation; PSD, Pattern Standard Deviation; cpRNFL, circumpapillary Retinal Nerve Fiber Layer; GCC, Ganglion Cell Complex; FLV, Focal Loss Volume; GLV, Global Loss Volume; ONH, Optic Nerve Head; wiVD, whole image Vessel Density; idVD, inside disc Vessel Density; cpVD, circumpapillary Vessel Density; shVD, superior hemi Vessel Density; ihVD, inferior hemi Vessel Density; wiCD, whole image Capillary Density; idCD, inside disc Capillary Density; cpCD, circumpapillary Capillary Density; shCD, superior hemi Capillary Density; ihCD, inferior hemi Capillary Density; fVD, foveal Vessel Density; parafoVD, parafoveal Vessel Density; parafoshVD, parafoveal superior hemi Vessel Density; parafoihVD, parafoveal inferior hemi Vessel Density; paraftVD, parafoveal temporal Vessel Density; parafoSV, parafoveal superior Vessel Density; parafoNV, parafoveal nasal Vessel Density; parafoiVD, parafoveal inferior Vessel Density; perifVD, perifoveal Vessel Density; perifshVD, perifoveal superior hemi Vessel Density; perifiVD, perifoveal inferior hemi Vessel Density; periftVD, perifoveal temporal Vessel Density; perifsVD, perifoveal superior Vessel Density; perifnVD, perifoveal nasal Vessel Density; perifiVD, parafoveal inferior Vessel Density</p>				

Except for the nonsignificant correlation between wiCD of the ONH and MD of the VF 24 – 2 and wiCD of the ONH and idCD and MD of the VF 10 – 2, other vascular parameters in the ONH area had significant correlation (controlling for patient, age, gender, SSI and disc area) with MD of VF 24 – 2 and 10 – 2 (Table 3). Whole image vessel density, ihVD and shCD had the strongest correlation with the MD of VF 24 – 2 ($r = .649$, $r = .529$, $r = .520$, respectively; $p < .001$) (Table 3) (Fig. 1). circumpapillary vessel density, shCD and shVD were the factors with strongest correlation with the MD of the VF 10 – 2 ($r = .445$, $p < .001$; $r = .441$, $p < .001$ and $r = .382$, $p = .003$; respectively) (Table 3) (Fig. 1). Among macular vascular parameters perifiVD ($r = .397$; $p = .002$) (Fig. 1), perifiVD ($r = .373$; $p = .004$) and perifshVD ($r = .361$; $p = .006$) had the strongest correlation with the MD of VF 24 – 2 (Table 3). Also, the same parameters had the strongest correlation with the MD of VF 10 – 2 ($r = .429$, $p = .001$; $r = .342$, $p = .010$; $r = .345$, $p = .009$; respectively) (Fig. 1) (Table 3).

Table 4 shows the AUC of different parameters to detection of the severity of glaucoma. Structural parameters related to cpRNFL and macula with greatest AUC were inferior cpRNFL, RNFL thickness in the superotemporal sector, superior cpRNFL, superior GCC, FLV and GLV (AUC = .789, AUC = .779, AUC = .765, AUC = .818, AUC = .811, AUC = .789; $p < .001$). Vascular parameters with greatest AUC were ihVD, wiVD and shVD in the ONH area and perifiVD, perifiVD and ihVD in SCP of the macula (AUC = .886, AUC = .869, AUC = .868, AUC = .833, AUC = .825, AUC = .815; $p < .001$). Global and average parameters in each of the imaging modalities and structural and vascular parameters with greatest AUCs are shown in Fig. 2.

Table 4

The prediction ability of different structural parameters to detect the severity of glaucoma.

	Area Under the Curve	Standard Error	Asymptotic Significance	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
Average cpRNFL	.666	.068	.025	.532	.800
Superior cpRNFL	.765	.058	< .001	.651	.879
Inferior cpRNFL	.789	.056	< .001	.679	.899
cpRNFL, Temporal Quadrant	.686	.065	.012	.558	.814
cpRNFL, Superior Quadrant	.750	.062	0.001	0.628	0.782
cpRNFL, Nasal Quadrant	.668	.069	.023	.532	.804
cpRNFL, Inferior Quadrant	.759	.061	< .001	.640	.878
cpRNFL, Temporal Upper	.678	.067	.016	.547	.809
cpRNFL, Superotemporal	.779	.057	< .001	.667	.891
cpRNFL, Superonasal	.743	.064	.001	.618	.868
cpRNFL, Nasal Upper	.667	.071	.024	.529	.805
cpRNFL, Nasal Lower	.633	.069	.073	.498	.768
cpRNFL, Inferonasal	.729	.062	.002	.608	.850
cpRNFL, Inferotemporal	.750	.067	.001	.618	.882
cpRNFL, Temporal Lower	.670	.068	.022	.537	.803
Average GCC	.784	.058	< .001	.670	.898
GCC, Superior	.818	.052	< .001	.717	.919
GCC, Inferior	.728	.066	.002	.599	.857
GCC, FLV	.811	.057	< .001	.699	.923
GCC, GLV	.789	.057	< .001	.677	.901
ONH wiVD	.869	.047	< .001	.777	.961

		Area Under the Curve	Standard Error	Asymptotic Significance	Asymptotic 95% Confidence Interval	
					Lower Bound	Upper Bound
	idVD	.662	.067	.028	.530	.795
	cpVD	.837	.051	< .001	.736	.938
	shVD	.868	.046	< .001	.779	.957
	ihVD	.886	.041	< .001	.805	.967
	wiCD	.673	.068	.020	.540	.806
	idCD	.664	.067	.027	.532	.796
	cpCD	.807	.057	< .001	.696	.918
	shCD	.831	.050	< .001	.734	.928
	ihCD	.823	.051	< .001	.724	.923
Macula	wiVD	.720	.065	.004	.593	.847
	shVD	.784	.065	< .001	.657	.911
	ihVD	.815	.058	< .001	.700	.929
	wETDRSVD	.797	.066	< .001	.667	.926
	fVD	.637	.073	.070	.493	.780
	parafVD	.531	.076	.681	.383	.679
	parafshVD	.762	.068	.001	.628	.895
	parafihVD	.768	.066	< .001	.638	.898
	paraftVD	.704	.071	.006	.566	.843
	parafsVD	.719	.069	.003	.585	.854
	parafnVD	.686	.081	.014	.526	.845
	parafiVD	.671	.072	.021	.530	.812
	perifVD	.765	.067	< .001	.634	.895
	perifshVD	.780	.065	< .001	.653	.907
	perifihVD	.825	.056	< .001	.716	.934
	PeriftVD	.789	.064	< .001	.664	.915
	PerifsVD	.770	.065	< .001	.642	.898

	Area Under the Curve	Standard Error	Asymptotic Significance	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
perifnVD	.768	.060	< .001	.650	.886
perifiVD	.833	.049	< .001	.736	.930
cpRNFL, circumpapillary Retinal Nerve Fiber Layer; GCC, Ganglion Cell Complex; FLV, Focal Loss Volume; GLV, Global Loss Volume; ONH, Optic Nerve Head; wiVD, whole image Vessel Density; idVD, inside disc Vessel Density; cpVD, circumpapillary Vessel Density; shVD, superior hemi Vessel Density; ihVD, inferior hemi Vessel Density; wiCD, whole image Capillary Density; idCD, inside disc Capillary Density; cpCD, circumpapillary Capillary Density; shCD, superior hemi Capillary Density; ihCD, inferior hemi Capillary Density; fVD, foveal Vessel Density; parafoVD, parafoveal Vessel Density; parafoshVD, parafoveal superior hemi Vessel Density; parafoihVD, parafoveal inferior hemi Vessel Density; paraftVD, parafoveal temporal Vessel Density; parafoSV, parafoveal superior Vessel Density; parafoNV, parafoveal nasal Vessel Density; parafoiVD, parafoveal inferior Vessel Density; perifVD, perifoveal Vessel Density; perifshVD, perifoveal superior hemi Vessel Density; perifihVD, perifoveal inferior hemi Vessel Density; periftVD, perifoveal temporal Vessel Density; perifsVD, perifoveal superior Vessel Density; perifnVD, perifoveal nasal Vessel Density; perifiVD, parafoveal inferior Vessel Density					

Table 5 and Table 6 are related to the comparison of the AUC of the different parameters. Among global and average variables only wiVD in the ONH are had greater AUC than average cpRNFL (.869 versus. .666; $p = .001$). As presented in Table 6 in the pairwise comparison of the variables with the greatest AUC no significant difference was found.

Table 5

Comparison between area under the curve between global structural and vascular parameters.

	GCC, GLV	ONH, wiVD	Macula, wiVD
Average cpRNFL	.165	.001	.654
GCC, GLV		.212	.481
ONH, wiVD			.057
GCC, Ganglion Cell Complex; GLV, Global Loss Volume; ONH, Optic Nerve Head; wiVD, whole image Vessel Density; cpRNFL, circumpapillary Retinal Nerve Fiber Layer			

Table 6

Comparison between the area under the curve in different structural and functional parameters with the highest area.

	GCC, Superior	ONH, ihVD	perifiVD
Inferior cpRNFL	.587	.056	.440
GCC, Superior		.163	.658
ONH, ihVD			.601
GCC, Ganglion Cell Complex; ONH, Optic Nerve Head; ihVD, inferior hemi Vessel Density; perifiVD, perifoveal inferior Vessel Density; cpRNFL, circumpapillary Retinal Nerve Fiber Layer			

Discussion

In the current investigation, we showed that circumpapillary vessel and capillary density and macular vessel density have a stronger positive correlation with the MD of VF 24 – 2 and 10 – 2 than structural parameters related to cpRNFL and macula. Also, our study showed that vascular parameters have greater accuracy for the detection of the severity of glaucoma.

Intraocular pressure is the most significant risk factor for the development and progression of glaucoma [19]. The goal of the current medical and surgical treatments is the reduction of the IOP for preventing progression. The deterioration of the VF and RNFL may occur despite proper IOP reduction, so other mechanisms besides IOP have been postulated for glaucoma [20]. Since there is an association between diabetes, systemic hypertension, autoimmune diseases, Raynaud's phenomenon, migraine, and glaucoma a vascular theory is highly possible [21–24]. Optical coherence tomography angiography provides a non-invasive and 3-dimensional evaluation of retinal and choroidal microvasculature in different conditions including glaucoma.

Decreasing vascular density in the continuum of the POAG had been the subject of various studies. In a study by Yarmohammadi et al. wiVD, cpVD and global RNFL were compared between healthy, glaucoma suspects and glaucomatous eyes. Whole image vessel density, cpVD, and average RNFL were significantly lower in glaucoma and wiVD had the greatest accuracy for differentiating glaucoma and glaucoma suspects from healthy eyes [25]. In another study by Kumar et al., the discriminant function of the vascular parameters for determining disease severity was evaluated. They enrolled normal and both POAG and primary angle-closure glaucoma (PACG) eyes with different severities in their investigation. They found a lower inside disc VD and en face VD in the RPC slab in the glaucomatous eyes in comparison to the normal eyes. Also, the VD between different stages of glaucoma was different [26]. Geyman and his colleagues showed decreasing perfused capillary density of the ONH by worsening the stage of the POAG [27]. In our study eyes with advanced glaucoma had lower vessel density in different areas except for idVD. By automated removal of the large vessels eyes with advanced glaucoma had lower wiCD, shCD, and ihCD. The interesting finding was the non-significant difference in the average RNFL thickness between moderate and advanced stages of glaucoma probably due to reaching the floor

while the vascular parameters of the ONH showed significant difference. Considering macular vascular parameters, Rao et al showed lower VD of the whole image and different quadrants of the parafoveal regions in the SCP of POAG eyes in comparison to the normal subjects in two different studies [28, 29]. We showed lower wiVD and in the temporal, superior, and nasal quadrants of the perifoveal region in eyes with advanced glaucoma. There was no significant difference in the VD of different quadrants of the parafoveal region.

Generally, in our study, the correlation between vascular parameters and the MD of the VF 24 – 2 and 10 – 2 was stronger than the correlation between structural parameters and the MD of visual fields, similar to previous studies [30, 31]. This finding shows the importance of VD in the functional status of glaucomatous patients. By taking into account the impaired blood supply as an etiology of POAG, it is meaningful that VD will drop earlier than the structural parameters in a stage in which the RGCs are dysfunctional but not atrophied [30]. In addition, we enrolled eyes with moderate and advanced glaucoma approaching the floor of the structural parameters while there may not be a detectable floor for vascular parameters [16]. Another finding in the current investigation was the stronger correlation of the vascular parameters of the ONH area with the MD of the VF 24 – 2 and VF 10 – 2 than the correlation between macular vascular parameters and the MD of VFs which is in concordance with Chen et al. study. As the macular vascular parameters don't seem to have a detectable floor the reason for this finding is unclear [16]. One possible explanation is that by assessment of the macula only a limited area of the vascular network is evaluated while the glaucomatous damage may originate beyond the macula which may be presented at the ONH area. A positive correlation between macular VDs and the MD of the VF 10 – 2 has been shown in a few studies [32, 33]. Unlike previous studies, in the current investigation, VDs were evaluated in a 6*6 mm² area centered on the fovea in both parafoveal and perifoveal regions. None of the VDs of the parafovea had a significant correlation with the MD of the VF 10 – 2 as opposed to periftVD, perifsVD, and perifiVD which had a significant positive correlation indicating more temporal and peripheral glaucomatous damage may occur even in moderate and advanced glaucoma.

We also evaluated the diagnostic accuracy of the different structural and vascular parameters for the detection of the severity of glaucoma. Generally, vascular parameters had greater AUC than structural parameters but in pairwise comparison of the parameters with the greatest AUCs in each category (structure and vasculature of the ONH and macula), there was no significant difference. In the pairwise comparison of the average cpRNFL, GLV, and wiVD of the macula and ONH, wiVD of the ONH area had greater AUC and better diagnostic accuracy for detection of the severity of the glaucomatous damage. Comparison of the vascular and structural parameters for discrimination between POAG and healthy eyes have mixed results in previous studies. Similar AUCs for differentiating glaucomatous eyes from normal subjects have been reported previously for cpVD and RNFL thickness [34]. Some studies have shown lower power for vasculature in comparison to structural parameters for discriminating POAG from normal eyes [29, 35–37]. The aforementioned studies have evaluated the power for discriminating POAG from normal eyes while we compared the power for discriminating moderate from advanced POAG eyes. We showed greater diagnostic accuracy for wiVD than average cpRNFL for detection of the severity of

glaucoma. As is expected in the later stages of the continuum of glaucoma, when the structure is approaching its floor the role of vasculature becomes more prominent.

Our study has certain limitations. First, we didn't record the axial length and systemic conditions in our study. Due to the substantial effects of the axial length on the VDs of the ONH area, it should be controlled in analyzing the correlation of the vascular and functional parameters [38]. Second, the sample size between our groups wasn't equal. Third, our study was cross-sectional. So, determining the impaired blood supply as the cause or consequence of the POAG was not possible.

In conclusion, we should say that vasculature has a stronger correlation than the structure with functional parameters in moderate and advanced glaucoma. Also, the accuracy of vascular parameters may be greater for discrimination of the moderate from advanced glaucoma.

Declarations

Funding: The authors received no financial support for the research, authorship, and/or publication of this article.

Conflicts of interest/Competing interests: Yadollah Eslami declares that he has no conflict of interest. Sepideh Ghods declares that she has no conflict of interest. Massood Mohammadi declares that he has no conflict of interest. Mona Safizadeh declares that she has no conflict of interest. Ghasem Fakhraie declares that he has no conflict of interest. Reza Zarei declares that he has no conflict of interest. Zakieh Vahedian declares that she has no conflict of interest. Seyed Mehdi Tabatabaei declares that he has no conflict of interest.

Availability of data and material: The data that support the findings of this study are available from the corresponding author, [SMT], upon reasonable request.

Code availability: Not Applicable.

Ethics approval: All procedures performed in this study which involve human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent to participate: Informed consent was obtained from all individual participants included in the study.

Consent for publication: There is no identifying information about participants available in the article, so this issue is not applicable.

Code availability: Not Applicable.

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Figures

Figure 1

Scatter plots of the strongest correlations between structural and vascular parameters and mean deviation of visual field 24-2 and 10-2

1A Correlation between superior circumpapillary retinal nerve fiber layer and mean deviation of the visual field 24-2

1B Correlation between the nasal quadrant of the circumpapillary retinal nerve fiber layer and mean deviation of the visual field 10-2

1C Correlation between superior ganglion cell complex and mean deviation of the visual field 24-2

1D Correlation

between superior ganglion cell complex and mean deviation of the visual field 10-2
 1E Correlation between whole image vessel density of the optic nerve head and mean deviation of the visual field 24-2
 1F Correlation between circumpapillary vessel density and mean deviation of the visual field 10-2
 1G Correlation between perifoveal inferior vessel density and mean deviation of the visual field 24-2
 1H Correlation between perifoveal inferior vessel density and mean deviation of the visual field 10-2

Figure 2

2A Receiver operating characteristic curve of the global structural and vascular parameters
 1B Receiver operating characteristic curve of the structural and vascular parameters with the greatest area under the curve