Correlation Between Peripapillary Retinal Nerve Fiber Layer Thickness And Optic Disc Parameters In Glaucoma Patients Using Optical Coherence Tomography

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Abstract:

Aim of study: To investigate the correlation between optic disc parameters (disc area and vertical cup disc ratio) and peripapillary retinal nerve fiber layer thickness and its value in evaluating glaucoma cases using optical coherence tomography.

Methods: this study included 35 eyes of 20 patients, 9 males and 11 females. 17 eyes as glaucoma cases and 18 control eyes (age: 51.8±10.85years old) were recruited at ophthalmology department at Benha university hospital. Complete ophthalmic assessment, visual field and OCT optic nerve imaging were done at the investigation unit of the department.

Results: Disc area (DA) values (M±SD) were 2.31± 0.34 and 2.69±0.51 for cases and control respectively (P value: 0.016). VCDR values (M±SD) were 0.67±0.16 and 0.62 ±0.14 for cases and control respectively (p value: 0.28). DA show only significant correlation to nasal PPRNFL thickness while VCDR show only significant negative correlation to average PPRNFL thickness. There is significant positive correlation between VCDR and DA. ROC curve analysis testing validity of DA and VCDR to predict glaucoma show high sensitivity (82.4%) and low specificity (61.1%) for DA (p value 0.009) and low sensitivity (58.8%) and low specificity (44.4%) for VCDR (p value 0.85).

Conclusion: VCDR may be an insensitive method for evaluating or monitoring glaucomatous functional damage in POAG or classifying its severity. Disc area significantly affects VCDR and may have a role in predicting POAG cases.

Key words: PPRNFL, peripapillary retinal nerve fiber layer, VCDR, disc area, POAG, optical coherence tomography (OCT).

Introduction:

Glaucoma is described as an optic neuropathy with associated visual function loss. Although elevated intraocular pressure (IOP) is the most important risk factors, it does not have a role in the definition of the disease. [(1)] The World Health Organization (WHO) estimated that glaucoma is the second commonest cause of blindness worldwide. [(2)]

A glaucoma suspect is defined as an adult who has at least one of the following findings in at least one eye: an optic nerve or nerve fiber layer (NFL) defect suggestive of glaucoma (enlarged cup–disc ratio (CDR), asymmetric CDR, notching or narrowing of the neuro-retinal rim, a disc hemorrhage or suspicious alteration in the NFL), a visual field abnormality consistent with glaucoma and an elevated IOP greater than 21 mm Hg. Usually, if two or more of these findings are present, the diagnosis of primary open angle glaucoma (POAG) is supported, especially in the presence of other risk factors such as age, a family history of glaucoma and the black race and no other secondary causes. The diagnosis of a glaucoma suspect and POAG is also dependent on a normal open angle on Gonioscopy. [(3)]

A magnified, preferably stereoscopic, examination of the optic disc using a 90 diopter (D) lens or a contact lens with the slit lamp is the ideal method of examining these structures. [(4)]

Vertical elongation of the optic cup is a characteristic feature of glaucomatous optic neuropathy. The vertical cup to disc ratio (VCDR) is a simple, robust indicator of glaucomatous loss of the neuroretinal rim. [(5)]

But many factors like histological structure of nerve axons and lamina cribrosa affect the disc size and CDR. [(6)](

Also, the ability of CDR to detect glaucoma is limited due to the wide variability of CDRs in the normal population. Such variability is explained, at least in part, by the significant relationship between the CDR and the size of the optic disc (OD). [(7, 8)]

In a study investigating correlation between CDR and retinal ganglion cell (RGC) concluded that assessment of CDR is an insensitive method for evaluation of progressive neural losses in glaucoma. [(9)]

Vertical cup disc ratio (VCDR) is also affected by optic disc size and axial length of the eye. The Sole use of VCDR percentile cut offs in defining glaucoma cases in population surveys requires further validation. [(10)]

Aim of the study:

To investigate the correlation between optic disc parameters (disc area and vertical cup disc ratio) and peripapillary retinal nerve fiber layer thickness and its value in evaluating glaucoma cases using optical coherence tomography.

Subjects and metods:

This Hospital-based cross sectional observational study included consecutive allocation of glaucoma suspects and primary open angle glaucoma as they presented to the specialized eye center at Benha university hospital.

20 participants were recruited and informed consent was taken from all. Inclusion criteria were glaucoma suspects with open angles on gonioscopy (grades III and IV Shaffer's' grading system), already diagnosed patients with primary open angle glaucoma or recent diagnosis of POAG. Exclusion criteria were angle closure glaucoma, secondary glaucoma, uncooperative patients and age below 18.

Participants were chosen from the General Ophthalmology Clinic on account of suspicious discs or elevated IOP after treatments for other ocular conditions. The best corrected visual acuity was measured. Participant's pupils were dilated using tropicamide 1% after intra-ocular pressure measurement by Goldmann applanation tonometry and gonioscopic examination. A slit lamp binocular indirect ophthalmoscopy using +78D / 90 D (Volks) lens was used to examine the optic nerve head and retinal nerve fiber layer. Participants with superficial splinter hemorrhage, focal loss of neuro-retinal rim (notching), generalized loss of neuro-retinal rim (VCDR ≥0.5), cup-disc ratio asymmetry (≥ 0.2) or loss of retinal nerve fibers were allowed to proceed with the study. Also participants whose optic nerve head and nerve fibers appeared normal but had IOP greater than 21 mmHg were also included.

Visual field was done to all cases using Carl Zeiss AG automated Humphrey perimeter, model 745i, made in Germany, using SITA strategy and 24-2 degree testing.

OCT were done to all study groups using SD (spectral domain) Topcon 3D OCT 2000, made in Japan, 2014. Optic disc topography and peripapillary retinal nerve fiber layer are imaged using 3D cubic of (6mmX6mm) area. Disc area is identified by detection of the RPE edges (disc detection points) and a reference surface connecting these points is made so disc area can be calculated. VCDR is measured as the ratio of height of the rectangle circumscribing cup area against the height of the rectangle circumscribing the disc area. PPRNFL is imaged and sectors are identified in clock hours or degrees. Superior sector is 45:135degree and accordingly each sector represents 90 degree.

Results

The study included 35 eyes of 20 patients, 9 males and 11 females, classified as 17 eyes of glaucoma patients and 18 eyes of non-glaucoma patients. The mean age for participants was 51.8±10.85 years old. Tables (1) and (2) show demographic data of included individuals.

Table (1) Distribution of the studied group according to personal factors.

	The studied group (35)	
	No	%
Gender		
Male	9	45.0
Female	11	55.0
Age mean ±SD , range		51.8±10.85, 20-67

Table (2) Comparison between case and control groups according to personal factors.

	Case group (9)		Control group (11)		Statistical test	P value
	No	%	No	%		
Gender						
Male	3	33.3	6	54.5	FET= 0.90	0.34
Female	6	66.7	5	45.5		
Age mean ±SD	55.44	6.64	48.82	12.91	St t=1.39	0.18

Comparison between clinical findings of cases and controls is demonstrated in table (3). IOP values was statistically significant (P value<0.001) with the mean for cases was 24.35±8.33 mmHg and for control was 14.22 ± 2.26 mmHg. CDR was 0.57±0.18 for cases while it was 0.56± 0.14 for controls with no statistical significance (P value: 0.79).

The data of OCT examination are illustrated in table (4). The mean disc area was 2.31± 0.34 for cases and 2.69±0.51 for control group and was statistically significant (P value: 0.016). The mean vertical CDR was 0.67±0.16 and 0.62 ±0.14 for cases and control respectively without statistical significance (p value: 0.28).the mean of average PPRNFL thickness was 72.94± 16.32 for cases and was 98.17±10.92 for control with statistical significance(| p value<0.001). inferior sector of PPRNFL was the thickest in case and control group with mean thickness of 88.35±33.86 and

Table (3): comparison between cases and control, clinical data

	Case group (17 eye)		Control group (18 eye)		Statistical test (st t test)	P value
	Mean	±SD	Mean	±SD		
BCVA	0.43	0.29	0.65	0.22	2.57	0.015*
Median (IR)	0.50(0.18-0.55)		0.50 (0.50-0.90)		MW=1.97	0.049*
IOP	24.35	8.33	14.22	2.26	4.97	<0.001**
CDR	0.57	0.18	0.56	0.14	0.28	0.79
Gonioscopy :						
G2	2	11.8	0	0.0	FET= 2.25	0.23
G3	15	88.2	18	100		
Lens :						
NAD	4	23.5	7	38.9	FET= 4.88	0.30
Ns	9	52.9	6	33.3		
N1	2	11.8	3	16.7		
PS	2	11.8	0	0.0		
PSCC	0	0.0	2	11.1		
Pupil :						
RRR	14	82.4	18	100	FET= 1.59	0.104
Sluggish	3	17.6	0	0.0		
Fundus finding :						
PPRNFL Defect	4	23.5	0	0.0	FET= 6.51	0.008**
Myopic crescent	2	11.8	0	0.0		
No abnormalities	11	64.7	18	100		

BCVA: Best corrected visual acuity. IOP: intraocular pressure. CDR: cup disc ratio. NAD: no abnormality detected. Ns: nuclear sclerosis. N1: nuclear cataract grade 1. RRR: round regular and reactive. PPRNFL: peripapillary retinal nerve fibre layer.

118.5±13.51 for case and control respectively and was statistically significant(p value 0.001). Superior PPRNFL mean thickness was 81.06±28.47 and 119.5±15.94 for cases and control respectively with statistical significance (p value <0.001). Nasal PPRNFL mean thickness was 63.76±15.15 and 86.83±16.27 for cases and control respectively with statistical significance (p value <0.001).Temporal PPRNFL mean thickness was 58.24±14.7 and 68.17±13.68 for cases and control respectively with the least statistical significance (p value 0.046).

Visual field examination was done and revealed arcuate scotoma as the most common finding (41.2%). Results of visual field examination are presented in table (5).

Table (4): comparison between cases and control, OCT finding

	Case group (17 eye)		Control group (18 eye)		Statistical test (st t test)	P value
	Mean	±SD	Mean	±SD		
Disc area	2.31	0.34	2.69	0.51	2.54	0.016*
Cup area	1.01	0.26	1.13	0.54	0.84	0.41
Vertical CDR	0.67	0.16	0.62	0.14	1.09	0.28
Inferior PPRNFL	88.35	33.86	118.5	13.51	3.5	0.001**
Superior PPRNFL	81.06	28.47	119.5	15.94	4.97	<0.001**
Nasal PPRNFL	63.76	15.15	86.83	16.27	4.34	<0.001**
Temporal PPRNFL	58.24	14.7	68.17	13.68	2.07	0.046*
Average thickness	72.94	16.32	98.17	10.92	5.4	<0.001**

Table (5): visual field finding of the case group

	Case group (17 eye)	
	No	%
Arcuate scotoma	7	41.2
Borderline	2	11.8
Para central scotoma	1	5.9
Tubular field	1	5.9
Nasal step	2	11.8
Insignificant	4	23.5

Correlation between optic disc parameters, clinical and OCT variables for case and control groups was done using r-test. Correlation is considered statistically significant when p value is less than 0.05.

In the case group, Disc area was inversely correlated to BCVA, IOP and VCDR with only statistical significance for VCDR. Disc area was directly correlated to average PPRNFL thickness and to all sectors of PPRNFL except temporal one. It is only statistically significant to nasal sector. Correlation between disc area and other variables in the case group is shown in table (6).

Table (6): correlation between disc area and clinical and OCT variables for case group.

Case group (17)	Disc area	
	Statistical test (r test)	P value
BCVA	-0.40	0.12
IOP	-0.24	0.37
Cup area	0.23	0.38
Vertical CDR	-0.50	0.043*
Inferior PPRNFL	0.34	0.18
Superior PPRNFL	0.45	0.068
Nasal PPRNFL	0.68	0.003**
Temporal PPRNF	-0.29	0.26
Average thickness	0.46	0.064

Results of correlating VCDR measured by OCT to clinical data and other OCT variables are presented in table (7). VCDR is inversely correlated to BCVA and IOP without statistical significance. It is directly correlated to CDR assessed clinically with strong statistical significance. VCDR was directly correlated to cup area without statistical significance. VCDR was inversely correlated to average PPRNFL and all sector thickness but only statistically significant for the average thickness.

Table (7): correlation between VCDR measured by OCT to clinical data and other OCT variables in case group.

Case group (17)	Vertical CDR	
	Statistical test (r test)	P value
BCVA	-0.09	0.74
IOP	-0.053	0.84
CDR	0.78	<0.001**
Cup area	0.43	0.083
Inferior PPRNFL	-0.41	0.10
Superior PPRNFL	-0.38	0.13
Nasal PPRNFL	-0.46	0.06
Temporal PPRNFL	-0.21	0.41
Average thickness	-0.56	0.021*

In the control group, table (8) shows that disc area is inversely correlated to BCVA with no statistical significance. It is directly correlated to cup area, VCDR, average PPRNFL and all other sector thickness with only statistical significance to average and temporal thickness.

Table (8): correlation between disc area and clinical & OCT variables in control group.

Control group (18)	Disc area	
	Statistical test (r test)	P value
BCVA	-0.13	0.60
IOP	0.14	0.58
Cup area	0.60	0.009**
Vertical CDR	0.13	0.60
Inferior PPRNFL	0.24	0.35
Superior PPRNFL	0.36	0.15
Nasal PPRNFL	0.25	0.31
Temporal PPRNFL	0.54	0.021*
Average thickness	0.47	0.05*

Table (9) presents correlation between VCDR measured by OCT to clinical data and other OCT variables in control group. VCDR was directly correlated to BCVA, IOP, CDR and cup area but only statistically significant for CDR and cup area. It was inversely correlated to PPRNFL thickness, average and all sectors with no statistical significance.

To test validity of optic disc parameters (disc area and VCDR) in glaucoma prediction, ROC curves and chi square test (x2) statistical test was done.

Table (10) and figure (1) show validity of disc area in prediction of glaucoma. A disc area more than 2.62 m2 (cut-off point) can predict development of glaucoma with statistical significance (95%CI 0.712 (0.535-0.89), p value 0.009) with high sensitivity (82.4%) and low specificity (61.1%).

Table (9): correlation between VCDR measured by OCT to clinical data and other OCT variables in control group.

Control group (18)	Vertical CDR	
	Statistical test (r test)	P value
BCVA	0.28	0.26
IOP	0.05	0.84
CDR	0.97	<0.001**
Cup area	0.82	<0.001**
Inferior PPRNFL	-0.08	0.75
Superior PPRNFL	-0.45	0.06
Nasal PPRNFL	-0.35	0.16
Temporal PPRNFL	-0.17	0.51
Average thickness	-0.36	0.14

Table (10): Validity of disc area in prediction of glaucoma.

	Case group (17 eye)		Control group (18 eye)		Statistical test (x^2)	P value
	No	%	No	%		
≤2.62	14	82.4	7	38.9	6.88	0.009**
>2.62	3	17.6	11	61.1		
AUC (95%CI)	0.712 (0.535-0.89)					
Cut-off point	2.62 m2					
Sensitivity	82.4%					
Specificity	61.1%					
PPV	66.7%					
NPV	78.6%					
Accuracy	71.4%					

Figure (1): Validity of disc area in prediction of glaucoma.

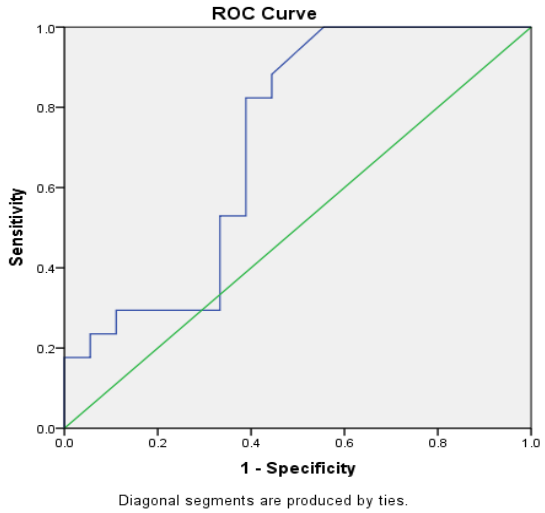
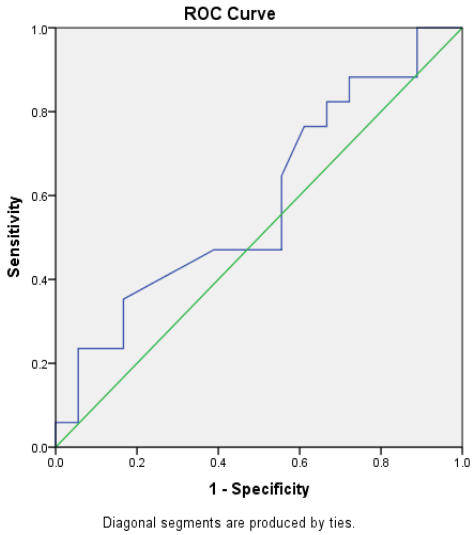


Table (11) and figure (2) show results of testing validity of VCDR to predict glaucoma development. It shows that VCDR more than 0.63 (cut-off point) can be associated with glaucoma development but with no statistical significant (95% CI 0.585 (0.393-0.777), p value 0.85). it has also low sensitivity (58.8%) and low specificity (44.4%).

Table (11): Validity of VCDR in prediction of glaucoma.

	Case group (17 eye)		Control group (18 eye)		Statistical test (x^2)	P value
	No	%	No	%		
≥0.63	10	58.8	10	55.6	0.04	0.85
<0.63	7	41.2	8	44.4		
AUC (95%CI)	0.585 (0.393-0.777)					
Cut-off point	0.63%					
Sensitivity	58.8%					
Specificity	44.4%					
PPV	50.0%					
NPV	53.3%					
Accuracy	51.4%					

Figure (2): Validity of VCDR in prediction of glaucoma.



To test impact of increasing VCDR measured by OCT on the thickness of PPRNFL in case and control group, VCDR is categorized into 3 categories as shown in tables 12 and 13. Category 1 includes VCDR less than 0.5. Category 2 includes VCDR 0.5:0.7. Category 3 includes VCDR more than 0.7.

Table (12) shows effect of increasing VCDR on PPRNFL thickness in case group. It shows that PPRNFL thickness, average and all sectors, decreases by transitioning from category 1 to 2 to 3 but with no statistical significance. Inferior and superior PPRNFL are the most affected especially when transition from category 1 to 2. Inferior PPRNFL shows decrease by mean percent of 35.05% while superior PPRNFL thickness shows decrease by mean percent of 35.98% from category 1 to 2. Transition from category 2 to 3 was associated with less decrease in PPRNFL thickness.

Table (12): effect of increasing VCDR on PPRNFL thickness in case group.

Vertical C/D	Cat I (<0.5)		Cat II (0.5-0.7)		Cat III (>0.7)		Statistical test (ANOVA)	P value
	Mean	±SD	Mean	±SD	Mean	±SD		
Inferior	127.5	33.23	82.8	33.27	83.8	30.83	1.64	0.23
Superior	119.5	7.78	76.5	24.22	74.8	32.67	2.45	0.12
Nasal	73.5	20.51	66.7	13.12	54.0	15.41	1.81	0.20
Temporal	55.5	3.54	62.2	17.28	51.4	9.37	0.93	0.42
Average thickness	93.5	10.61	72.5	12.94	65.6	19.51	2.49	0.12

Table (13) shows effect of increasing VCDR on PPRNFL thickness in control group. It shows no statistical significance except for differences of nasal PPRNFL thickness. In this study, VCDR category 1 (less than 0.5) represents 16.66% of control group. VCDR of category 2 (0.5:0.7) represent 66.66% of normal control eyes with normal PPRNFL thickness. Category 3 (VCDR more than 0.7) represents 16.66% with normal PPRNFL thickness.

Table (13): effect of increasing VCDR on PPRNFL thickness in control group.

Vertical C/D	Cat I (<0.5) (3)		Cat II (0.5-0.7) (12)		Cat III (>0.7) (3)		Statistical test (ANOVA)	P value
	Mean	±SD	Mean	±SD	Mean	±SD		
Inferior	122.33	18.77	115.75	11.69	125.67	17.39	0.77	0.48
Superior	136.0	9.54	113.92	14.21	125.33	17.67	3.2	0.069
Nasal	108.33	19.86	82.33a	12.52	83.33a	12.66	4.41	0.031*
Temporal	72.0	10.0	66.83	14.36	69.67	17.93	0.17	0.84
Average thickness	109.33	9.61	94.67	9.39	101.0	12.76	2.76	0.095

(a):significant with category I

Discussion

Optic nerve head and PPRNFL thickness changes are one of the important criteria to diagnose and follow up POAG. [3] Average and regional PPRNFL of the control group are similar to that found in other studies like Alasil T et al. [11] Average and regional PPRNFL of the case group are below normal values and were statistically significant.

VCDR is a very important clinical tool being most affected in glaucoma patients due to its histological variation in superior and inferior poles of the disc and more affected by mechanical and vascular damage. [12]

In our study, mean VCDR was0.67±0.16 and 0.62 ±0.14 for cases and control respectively without statistical significance (p value: 0.28). Mean VCDR for control group is higher than recorded in other studies. Andrew et al reported mean VCDR to be 0.45 for normal people and J G Crowston et al reported it to be 0.43 and reported statistical significance when compared to that of glaucomatous eyes. [9, 10] This may be attributed to small number of our sample and needs more sample size to give more reliable results.

Mean VCDR for case group was near values reported in previous studies like Andrew et al (0.62) and Willekens K et al (0.69). [9, 13]

VCDR is considered to be a good tool to diagnose glaucomatous changes since 1960 by Snydacker D et al and supported by recent studies like George ACF et al, Thomas R et al and Willekens K et al. [3, 4, 13, 14] Our study results revealed negative correlation between VCDR and PPRNFL thickness that was only statistically significant with the average PPRNFL thickness. For the control group, this correlation was insignificant statistically except with nasal sector which was directly correlated to VCDR.

Andrew J et al studied the relationship of VCDR to RGC layer and found that VCDR is an insensitive tool to assess glaucoma progression. [9] Also, J G Crowston et al recommended further validation of VCDR to use it for diagnosis of glaucoma. [10] while Foster PJ et al reported that VCDR is a good factor to diagnose and monitor glaucoma cases. [5] The debate about the role of VCDR in diagnosis and monitoring glaucoma cases may be due to wide variability of the VCDR in normal population and its affection by the optic disc size. [7, 8] Garway-Heath DF et al found significant direct correlation between VCDR and disc size.[7] This is supported by our finding that found disc a statistically significant direct correlation between disc area and VCDR in the case group (table 6).

VCDR may not reflect the damage in PPRNFL as it is affected mechanically by the high IOP and the histological variability of lamina cribrosa structure that may play a role in VCDR variability among patients. [12] A similar finding occurs in cases with congenital glaucoma in which a large cup is noted with high IOP that may return to normal after IOP control. [15] Also the microvasculature of the optic disc and regional blood supply of lamina cribrosa and the disc may play a role in glaucomatous damage and its affinity to specific areas in the disc. [16, 17]

In our study, validity of disc area and VCDR to predict glaucoma cases was tested using ROC curves and chi square test (x2) statistical tests. In this study disc area show statistically significant high sensitivity (82.4%) but moderate specificity (61.1%) on a basis of cut off value of 2.62 mm2. VCDR show non-statistically significant results with moderate sensitivity (58.8%) and low specificity (44.4%). Stuart K et al shows in his study that disc area and VCDR can be good predictors for glaucoma progression and functional damage in glaucoma. [18] Larrosa JM et al study validity of PPRNFL and optic disc parameters in diagnosing and monitoring glaucoma and show high sensitivity/specificity (80.5/80.7%) for inferior PPRNFL and these values was 61.2% sensitivity and 89.1% specificity for VCDR. [19] This results are heterogeneous regarding diagnostic accuracy of VCDR, disc area and PPRNFL thickness so, it needs further studies to evaluate such parameters.

On studying the effect of increasing VCDR on the PPRNFL thickness in case group (table 12), It shows that PPRNFL thickness, average and all sectors, decreases by transitioning from category 1 to 2 to 3 but with no statistical significance. Inferior and superior PPRNFL are the most affected especially when transition from category 1 to 2. Inferior

PPRNFL shows decrease by mean percent of 35.05% while superior PPRNFL thickness shows decrease by mean percent of 35.98% from category 1 to 2. Transition from category 2 to 3 was associated with less decrease in PPRNFL thickness. On studying similar relation in the control group (table 13), It shows no statistical significance except for differences of nasal PPRNFL thickness. In the control group, VCDR category 1 (less than 0.5) represents 16.66% of control group. VCDR of category 2 (0.5:0.7) represent 66.66% of normal control eyes with normal PPRNFL thickness. Category 3 (VCDR more than 0.7) represents 16.66% with normal PPRNFL thickness. This results indicate that severity classification of glaucoma cases depending on VCDR assessment may be inaccurate and needs more evaluation.

Conclusion

At the end we can conclude that assessment of VCDR alone may be insensitive method for evaluating or monitoring glaucomatous functional damage in POAG. VCDR may reflect only functional damage to average PPRNFL thickness. Disc area significantly affects VCDR and may have a role in predicting POAG cases. Also, VCDR is inaccurate method to classify POAG cases. Further studies are needed with more sample size and concentration on individual follow up for validating our results. Also, more large studies are needed to test diagnostic accuracy, sensitivity and specificity of optic disc parameters in evaluating glaucoma cases.

Disclosure

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