

The Distribution of Vertical Cup-to-Disc Ratio and its Determinants in the Iranian Adult Population

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Abstract

Purpose: To determine the distribution of vertical cup-to-disc ratio (VCDR) and its relationship with ocular biometric indices.

Methods: This study was conducted in 4737 individuals aged 45-69 years living in Shahrood who participated in the second phase of Shahrood Eye Cohort Study in 2014. All participants underwent eye examinations including the measurement of visual acuity and refraction, slit-lamp biomicroscopy, retinal examination, and fundoscopy. Normality index was used to describe data distribution, and a multiple beta regression, with adjustment for the effect of cluster sampling, was applied to explore the relationship between VCDR and the study variables.

Results: The mean [95% confidence interval (CI)] VCDR was 0.297 (0.293-0.301) in all participants; 0.296 (0.291-0.302) in men and 0.297 (0.292-0.302) in women. The highest mean VCDR was seen in the age group 55-59 years (0.299, 95% CI: 0.292-0.307). The 97.5th percentile was 0.600. According to multiple beta regression analysis, VCDR had a positive association with the female sex ($P = 0.028$), spherical equivalent ($P < 0.001$), cigarette smoking ($P = 0.020$), and axial length ($P < 0.001$), and had a negative association with hypertension ($P = 0.001$), best corrected visual acuity ($P < 0.001$), hyperlipidemia ($P = 0.029$) and anterior chamber depth ($P = 0.001$).

Conclusions: The mean VCDR and the 97.5th percentile were lower than most other studies. Although ethnicity and race may play a role in this difference, this difference should be considered in clinical decisions in the current population.

Keywords: Cohort study, Glaucoma, Optical coherence tomography, Vertical cup-to-disc ratio

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INTRODUCTION

Estimates indicate that glaucoma is responsible for more than 2% of all visually impaired cases worldwide. It mostly affects the elderly, and since the aging population is growing rapidly in most countries, the prevalence of glaucoma is expected to increase in the future.¹

Different definitions and methods are used for the diagnosis of glaucoma, including a thinning of neuroretinal rim width,² visual field defect,³ vertical cup-to-disc ratio (VCDR)

asymmetry,⁴ increased intraocular pressure (IOP),⁵ and optical coherence tomography (OCT) findings.¹ However, a definite diagnosis of glaucoma is sometimes a matter of debate among ophthalmologists.

Glaucoma patients usually have a higher VCDR compared to normal people because the optic nerve is under pressure in these patients, increasing the VCDR.^{4,6} However, there is a significant overlap in VCDR between healthy individuals and

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glaucoma patients.^{7,8} Studies have shown that VCDR, with a sensitivity of 80% and specificity of 98%, is a very good method for diagnosis of glaucoma,⁹ but differentiation of healthy people from glaucoma patients requires a certain cut-off value in every population. The International Society for Geographic and Epidemiologic Ophthalmology (ISGEO) has proposed the VCDR 97.5th percentile as a cut-off value for diagnosis of glaucoma;¹⁰ nonetheless, due to differences in the distribution of VCDR in different populations, its value depends on ethnicity and other determinants.⁴ On the other hand, identification of different determinants of VCDR helps clinicians to make sound diagnostic and therapeutic decisions during ocular examination.⁶

Although local studies have been conducted in different countries to determine the distribution of VCDR,^{2-6,8,9,11-19} only one study has been performed for this purpose in Iran,²⁰ and therefore, there is a need for further research to provide more information on the distribution of VCDR. Our team set up a cohort study in people aged 40-64 years in Shahroud in recent years, which has provided researchers with valuable information on ocular indices. This cohort has made it possible to evaluate VCDR in an Iranian representative sample. Considering lack of information in this regard, we decided to conduct a study to determine the distribution of VCDR in this population according to age and sex and investigate its association with some biometric parameters.

METHODS

The present study was the second phase of Shahroud Eye Cohort Study, conducted in people from 45 to 69 years of age. The sampling details of the first phase were previously reported;²¹ however, they are mentioned briefly here. In the first phase, which started in 2009, random stratified cluster sampling was applied to select 300 clusters in Shahroud. Each health care center was considered a stratum. Then 300 clusters, with at least 20 people in each cluster, were selected randomly. The number of clusters inside each stratum was proportional to the population size of stratum. By beginning from the first house in each cluster, all people aged between 40 and 64 years were invited to participate. In the first phase, 6311 people were invited, of whom 5190 participated in the study (response rate = 82.2%). The second phase was performed in 2014 with participation of 4737 out of 5190 individuals who participated in phase 1. The Ethics Committee of Shahroud University of Medical Sciences approved the study protocol, which was conducted in accord with the tenets of the Declaration of Helsinki. Written informed consent was obtained from participants in both phases, and their demographic data were collected. Then participants underwent optometric tests, ophthalmologic examinations, and OCT imaging.

Non-cycloplegic refraction was performed using the ARK-510A Nidek auto refractometer. In the next step, distance and near uncorrected visual acuity were measured, and the results of auto refraction were refined using the Heine Beta 200 retinoscope. Using these data, distance and near

subjective refraction were done if visual acuity was not 20/20. Slit-lamp biomicroscopy was done using the Haag-Streit slit-lamp (Haag-Streit AG, Koeniz, Switzerland) by an ophthalmologist. IOP was measured using the Goldmann applanation tonometer. The Allegro Biograph (WaveLight AG, Erlangen, Germany) was used to measure biometric parameters and VCDR was determined by the ophthalmologist. A spherical equivalence (SE) of -0.5 diopter (D) or less was defined as myopia, and an SE of 0.5 D or more was considered hyperopia. VCDR was defined by a trained ophthalmologist (A.J.) during slit-lamp biomicroscopy.

The exclusion criteria were cataract grade >1, history of ocular trauma, corneal problems like scar and opacity, IOP >21 mmHg, history of any type of glaucoma in either eye, use of glaucoma medications, and corrected visual acuity worse than 20/40. Moreover, the data whose distance from the mean was more than 3 standard deviations were considered outliers and excluded from analysis.

Statistical analysis

Since VCDR showed a high correlation between fellow eyes ($r = 0.879$, $P < 0.001$), the data of the right eyes were used in analysis. Quantitative data are presented as mean and standard deviation. The central tendency indices and normality indices such as percentiles, skewness, and kurtosis were used to show the distribution of VCDR.

A multiple beta regression model was applied to evaluate the effect of different variables on VCDR.²² This method, which belongs to the exponential family, is used when the dependent variable (VCDR in this study) is a continuous variable ranging from 0 to 1. Logit link function and log-scale were used for modeling a set of predictors with the observed VCDR mean. For easy explanation of associations between variables, the elasticity value of each variable was calculated, which showed the amount of VCDR change for each 1% change in independent variables.

The effect of cluster sampling was considered in calculation of standard error. P values less than 0.05 were considered significant.

RESULTS

A total of 4737 people participated in phase 2 of study. After applying the exclusion criteria (including 89 people with glaucoma), the data of 3949 right eyes were analyzed. The mean age of these participants was 55.06 ± 5.96 years, and 58.6% of them ($n = 2315$) were women. Table 1 shows the mean and normality indices of VCDR in participants according to age, sex, and refractive error. Evaluation of normality indices showed that the 97.5th percentile, minimum, and maximum VCDR was 0.600, 0.000, and 0.800, respectively. The 2.5th, 5th, 25th, 75th, and 95th percentile was 0.100, 0.100, 0.300, 0.300, 0.300, and 0.500, respectively.

The mean (95% CI) VCDR was 0.297 (0.293-0.301) in participants, 0.296 (0.291-0.302) in men, and 0.297 (0.292-0.302)

in women. According to age group, the highest and lowest VCDR was seen in the age group 55-59 years (0.299, 95% CI: 0.292-0.307) and 65-69 years (0.289, 95% CI: 0.277-0.300), respectively. According to the refractive error, the highest and lowest VCDR was seen in emmetropic (0.300, 95% CI: 0.295-0.306) and myopic participants (0.291, 95% CI: 0.284-0.298), respectively.

Table 2 presents the results of multiple beta regression between VCDR and other variables. Male sex ($P = 0.019$), smoking ($P = 0.017$), increased SE ($P < 0.001$), and increased axial length (AL) ($P < 0.001$) had a positive correlation and hypertension ($P < 0.001$), increased best corrected visual acuity (BCVA) ($P < 0.001$), hyperlipidemia ($P = 0.029$), and increased anterior chamber depth (ACD) ($P = 0.002$) had an indirect correlation with VCDR.

Table 1: Distribution of vertical cup-to-disc ratio by sex, age, and refractive groups in 45-69-year-old population, Shahroud, Iran

Variables	Mean	95% CI
Total	0.297	0.293-0.301
Sex		
Male	0.296	0.291-0.302
Female	0.297	0.292-0.302
Age group		
45-49	0.297	0.290-0.305
50-54	0.296	0.290-0.303
55-59	0.299	0.292-0.307
60-64	0.296	0.288-0.304
65-69	0.289	0.277-0.300
Refractive groups		
Myopia	0.291	0.284-0.298
Emmetropia	0.300	0.295-0.306
Hyperopia	0.295	0.288-0.301

CI: Confidence interval

The results showed that 1% increase in SE and AL caused an increase of 0.0001 and 0.2571 in VCDR, respectively. Moreover, each 1% increase in ACD and BCVA was associated with a decrease of 0.0617 and 0.0005 in VCDR, respectively. Compared to men, VCDR was higher by 0.0233 in women. Hypertension and hyperlipidemia decreased VCDR by 0.0069 and 0.0035 and smoking increased VCDR by 0.0019, respectively. Other variables had no significant effect on VCDR.

DISCUSSION

This study showed that the variables of sex, SE, hypertension, smoking, BCVA, ACD, and AL were correlated with VCDR. Determination of the distribution of VCDR in different populations can present a clearer picture of the status of this index in the society, which is effective in diagnostic and therapeutic decisions.⁶ Table 3 shows the distribution of VCDR in some previous studies.

According to findings, the mean VCDR (95% CI) was 0.297 (0.293-0.301), which was close to values reported by Pakravan *et al.*²⁰ and Kim *et al.*¹¹ but lower than the results of some other studies.^{2,3,5,11,13,14,17,18,20,23} The reason for this difference may be differences in the age range of the participants, methods applied to measure VCDR, exclusion criteria, and ethnicity.

It should be noted that what is important in the distribution of VCDR is the 97.5th percentile in the normal population that is used as a cut-off point for diagnosis of glaucoma if there is a visual field defect.^{2,10} The 97.5th percentile was 0.60 in current study, 0.60 in another study conducted in Iran,²⁰ 0.68 in England and Australia,^{9,14} 0.7 in Japan,² Nigeria,¹⁶ and Bangladesh,¹⁸ 0.69 in the Netherlands,¹⁹ 0.63 in Germany³ and USA,⁴ and 0.8 in China.⁸ Although some studies have suggested the 99.5th percentile as the cut-off point, since there

Table 2: The association of vertical cup-to-disc ratio with explanatory variables and elasticity for each variable

Independent variables	Multiple beta regression		Change in VCDR by 1% change in covariate (elasticity)
	Coefficient (95% CI)	P	
Age (year)	-0.0003 (-0.0037 to 0.0031)	0.852	-0.0037 (-0.0433 to 0.0357)
Sex (male=0)	0.0674 (0.0071 to 0.1277)	0.028 ^a	0.0223 (0.0023 to 0.0423) ^a
Hypertension (no=0)	-0.0567 (-0.0898 to -0.0237)	0.001 ^a	-0.0069 (-0.0109 to -0.0029) ^a
Hyperlipidemia (no=0)	-0.0272 (-0.0517 to 0.0027)	0.029 ^a	-0.0035 (-0.0067 to 0.0003) ^a
Diabetics (no=0)	0.0296 (-0.0111 to 0.0704)	0.155	0.0013 (-0.0005 to 0.0031)
Smoking (no=0)	0.0653 (0.0104 to 0.1202)	0.020 ^a	0.0019 (0.0002 to 0.0035) ^a
Height (cm)	0.0009 (-0.0027 to 0.0045)	0.623	0.0304 (-0.0909 to 0.1518)
Weight (kg)	0.0010 (-0.0004 to 0.0024)	0.158	0.0158 (-0.0061 to 0.0378)
SE (diopter)	0.0278 (0.0134 to 0.0422)	<0.001 ^a	0.0001 (0.0001 to 0.0003) ^a
CCT (mm)	0.0001 (-0.0005 to 0.0005)	0.925	0.0028 (-0.0563 to 0.0620)
IOP (mm/Hg)	0.0039 (-0.0042 to 0.0120)	0.347	0.0104 (-0.0113 to 0.0321)
BCVA (logMAR)	-0.6036 (-0.8670 to -0.3403)	<0.001 ^a	-0.0005 (-0.0007 to -0.0003) ^a
ACD (mm)	-0.0955 (-0.1555 to -0.0356)	0.002 ^a	-0.0617 (-0.1005 to -0.0230) ^a
AL (mm)	0.0532 (0.0265 to 0.0799)	<0.001 ^a	0.2571 (0.1280 to 0.3862) ^a

^aSignificance. VCDR: Vertical cup-to-disc ratio, CI: Confidence interval, SE: Spherical equivalence, CCT: Central corneal thickness, IOP: Intraocular pressure, BCVA: Best corrected visual acuity, ACD: Anterior chamber depth, AL: Axial length

Table 3: Mean ± standard deviation and 97.5th percentile of vertical cap-disc ratio in different population-based studies

Author	Place	Publication year	Sample size	Age (years)	Mean ± SD	97.5 percentile
Kuang <i>et al.</i> ⁸	Taiwan, Chinese	2014	460	≥72	0.44±0.17	0.800
Carpel <i>et al.</i> ¹³	Minnesota, USA	1981	580	4-91	0.38	-
Amerasinghe <i>et al.</i> ⁶	Malay, Singapore	2008	3280	40-80	0.40±0.15	-
McClelland <i>et al.</i> ¹⁷	Ireland	2012	195	6-7	0.30±0.09	0.450 ^a
			225	12-13	0.37±0.09	0.650 ^a
Swanson ⁴	USA	2011	5575	≥40	-	0.630
Neubauer <i>et al.</i> ³	Munich, Germany	2005	106	≥40	0.30±0.18	0.630
Kim <i>et al.</i> ¹¹	Seoul, Korea	2015	17,767	≥19	0.34±0.12	-
Crowston <i>et al.</i> ¹⁴	Sydney, Australia	2004	6678	≥49	0.42±0.14	0.680
Ramrattan <i>et al.</i> ¹⁹	Rotterdam, Netherlands	1999	5114	≥55	0.49±0.14	0.690
Suh <i>et al.</i> ⁵	South Korean	2012	3191	≥40	0.41±0.14	-
Rahman <i>et al.</i> ¹⁸	Dhaka, Bangladesh	2004	2347	≥35	0.34±0.14	0.70
Buhrmann <i>et al.</i> ¹²	Kongwa, Tanzania	2000	3067	≥40	0.41±0.16	-
Garway-Heath <i>et al.</i> ⁹	London, England	1998	88	56.9±12.8 ^b	0.44±0.15	0.680
Jonas, <i>et al.</i> ¹⁵	Tamil Nadu, India	2003	70	47.5±8.7 ^b	0.56±0.08	-
Tsutsumi <i>et al.</i> ²	Kumejima, Japan	2012	3762	≥40	0.56±0.08	0.700
Kyari <i>et al.</i> ¹⁶	Nigeria	2015	851	≥40	0.4 ^c	0.7
Pakravan <i>et al.</i> ²⁰	Yazd, Iran	2017	1159	40-80	0.32±0.14	0.600
Current study	Shahroud, Iran		3030	45-69	0.29±0.10	0.600

^aUpper percentile (95%), ^bMean±SD, ^cMedian. SD: Standard deviation

are few people above this percentile (about 5 in 1000 eyes), the 97.5th percentile is more robust.

The 0.60 cut point for VCDR, had a sensitivity of 16.5% and a specificity of 99% in current study. Therefore only 16.5% of glaucomatous patients and 98.9% of normal people can be truly categorized by using VCDR.

Evaluation of VCDR in different age groups showed the lack of a distinct pattern for VCDR changes according to age in this study, which was also confirmed by multiple beta regression analysis. Although some studies have shown a direct association between VCDR and age,^{2,7,11,13,24} the magnitude of this association is higher in people below the age of 40 compared to the age group above 40 years. Therefore, the reason why we found no association between VCDR and age may be that participants of current study were all above 45 years of age. In fact in this age group, the healthy eyes do not undergo structural changes resulting in the ocular tissue growth. If there is a relationship between VCDR and age, it may be seen in younger participants whose eyes grow. However, Huynh *et al.*²⁵ found no association between VCDR and age in children. Some studies have shown that aging does not increase VCDR; it elevates IOP, which results in increased VCDR.¹¹ It seems that since participants susceptible to glaucoma and increased IOP were excluded from this study, this relationship was not observed.

The results showed a higher VCDR in women compared to men. Some studies have attributed this inter-gender difference of VCDR to differences in height and AL;¹¹ however, the association observed in this study was adjusted for age, height, weight, and other variables. Although a number of studies^{8,15,19} reported no association between sex and VCDR, some other studies showed a higher VCDR in men versus women,^{6,26}

which is in contrast to current findings. These inconsistencies underscore the need for further research in this regard.

Some studies have shown that increased height and decreased weight associated with increased VCDR.^{11,19} Although the exact mechanism of this association is not clear, a thinner neuroretinal rim²⁷ or increased IOP in these people may explain this relationship.²⁸ However, no relationship was found between VCDR with weight and height in this study, which is inconsistent with the results of the previously mentioned studies. Ramrattan *et al.*¹⁹ mentioned AL as a possible reason for this relationship since tall stature has a direct relationship with an increase in AL, and increased AL associated with a greater VCDR. The results of another study⁸ and current study confirmed this explanation because after adjusting for weight, height, and other variables, there was still a positive association between AL and VCDR in multiple beta regression model.

According to findings, each 1% increase in SE, increased the mean VCDR by 0.0001. This finding was in contrast to the results of some studies^{5,7,8,19,20,25} but consistent with the results of some other investigations.^{29,30} Although this inconsistency in the association between VCDR and SE is attributed to ethnic factors,¹⁷ some studies have reported that increased SE towards hyperopia decreases the rim, which is associated with an increase in VCDR.^{8,19} It should be noted that SE is a combination of AL, lens thickness, and corneal curvature, and these parameters need to be adjusted to determine the relationship of SE with VCDR. Moreover, in this study, VCDR had no association with central corneal thickness (CCT) and IOP, which is in line with other studies.^{8,20}

Similar to other studies,^{2,6,20} an inverse association was observed between hypertension and VCDR. Suh *et al.*⁵ reported

that hypertension increases the IOP, which applies pressure on the optic nerve resulting in decreased VCDR. However, the results of the current study and a study by Amerasinghe *et al.*⁶ rejected the above hypothesis because the effect of IOP was adjusted in the multiple model. Leske *et al.*³¹ showed that hypotension was associated with an increased risk of open-angle glaucoma, which could be due to decreased perfusion of the optic nerve. There are no other reports of the association of blood pressure and VCDR.^{6,8,20} However, Kim *et al.*¹¹ reported the hypertension increased VCDR, which is in contrast to the findings of this study.

Although trained ophthalmologist performed examinations, intra-observer variation and single rater may be limitations of this study. We also did not measure the disc area, which can be useful in evaluating small discs, and did not use color disc stereophotographs for this study. However, a large sample size, population-based design, and measurement of parameters by trained ophthalmologist and optometrists were the advantages of the present study.

In conclusion, the variables of sex, SE, hypertension, hyperlipidemia, smoking, BCVA, ACD, and AL correlated with VCDR independently and these associations were not affected by strong confounders like IOP, CCT, and age. Since little information is available about VCDR in the Iranian adult population, the results of this study can provide valuable information for clinical decision-making and early detection of at-risk people for glaucoma.

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Conflicts of interest

There are no conflicts of interest.

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