# Factors associated with Primary Open-angle Glaucoma in a Nepali Population: Jiri Eye Study

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#### ABSTRACT

**Introduction**: Glaucoma is the second most common cause of blindness with primary open-angle glaucoma (POAG) as one of the leading causes.

**Objective**: To study the ocular and systemic associated factors that lead to the development of primary open-angle glaucoma

Methodology: This is population-based, analytical cross-sectional, oculo-genetic study conducted from 2015 to 2018. Among the total 2042 study participants ≥18 years of age, included using convenience sampling, 37 were diagnosed with POAG. For comparative analysis, age and gender matched controls without glaucoma were selected in a 1:4 ratio from the same population. A detailed systemic and ophthalmic history was recorded; systemic and ophthalmic examinations were carried out. Examinations also included measurement of blood pressure and body mass index. A comprehensive ophthalmic examination included measurement of visual acuity, refraction, slit lamp bio microscopy, recording of intraocular pressure, gonioscopy and dilated fundus examination. Keratometry, biometry, visual field assessment, anterior and posterior segment Optical Coherence Tomography were undertaken.

Result: Prevalence of POAG among  $\geq$ 30 years was 2.53%, (males 0.98%, female 0.83%). The mean IOP was 15.34 ( $\pm$ 3.74) mmHg. Those  $\geq$ 40 years had an increased risk of developing POAG. POAG was associated with increased intraocular pressure (p = 0.019), increased vertical cup disc ratio (p <0.001), retinal nerve fibre layer thinning (p <0.001), increased pattern standard deviation (p <0.001) and decreased mean deviation (p = 0.020). Other factors such as BMI, DM, HTN, family history of glaucoma, smoking, alcohol consumption, tobacco chewing, refractive error, CCT, CCR, ACD, AL, lens thickness, and iris thickness were not associated.

**Conclusion**: Identifying the factors associated with POAG and adopting screening strategies for its early detection will prevent blindness in this population.

Key words: Associated factors; Jiri eye study; Nepal; population; prevalence; primary open-angle glaucoma.

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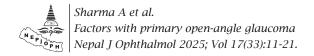
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## INTRODUCTION

Glaucoma is estimated to affect more than 60 million people worldwide and is the second most common cause of blindness (Quigley, 1996). Primary open-angle glaucoma (POAG) is one of the leading causes accounting for nearly three quarters (74%) of all glaucoma cases (Stewart et al., 2000) with a global prevalence of 3.05% (Tham et al., 2014).

The POAG is a multifactorial neurodegenerative condition where intraocular pressure (IOP) is the most important risk factor (Gordon et al., 2002). There are factors other than IOP which may be involved in the pathogenesis and progression of POAG, such as ocular and systemic risk factors (Leske, 2009). Ocular risk factors are refractive error, central corneal thickness (CCT), corneal curvature radius (CCR), iris thickness, anterior chamber depth (ACD), anterior chamber angle (ACA), lens thickness, axial length (AL), and myopia. Systemic risk factors are family history of glaucoma, systemic hypertension (HTN), diabetes mellitus (DM), body mass index (BMI) status, and behavioral risk factors such as cigarette smoking, alcohol consumption, and chewing tobacco. The occurrence of retinal nerve fibre damage despite normal IOP has led to the consideration that there are IOP independent risk factors contributing to the causation of the disease. Identification of these IOP independent associated factors will aid in the diagnosis and management of POAG.

The purpose of this study was to evaluate the ocular and systemic factors associated with POAG and other IOP independent factors. To the best of authors' knowledge, there are no population-based studies that have been

conducted in the past to evaluate the factors associated with POAG in Nepal.

# **METHODOLOGY**

The Jiri Eye Study is a population-based cross sectional oculo-genetic study conducted in Jiri. Jiri is a municipality in Dolakha District, Bagmati Province (previously in the Janakpur Zone), in north-eastern Nepal. It is approximately 190 kilometers east of Kathmandu. The study was conducted from 2015 to 2018. Convenience sampling technique was used. There were 2042 participants of age 18 years and above from seven different Jirel villages. All participants were informed about the study and a written informed consent was taken (fingerprints for illiterates). The Jirel pedigree is one of the most powerful documented human pedigree currently available for genetic studies (Williams-Blangero et al., 1990).

Among the 2042 study participants, 37 were diagnosed with primary open-angle glaucoma cases (High-Tension Glaucoma and Normal Tension Glaucoma). The control group comprised of age and gender matched participants in the ratio of 1:4. Patients with primary angle closure glaucoma, secondary glaucoma, pseudo exfoliation, glaucoma suspects, acute ocular infections, ocular tumors and trauma were excluded.

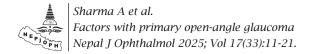
A detailed ocular and systemic history of HTN, DM, alcohol intake, smoking and tobacco chewing was taken. Height and weight measurements were recorded and the BMI status of an individual was calculated (defined as body weight in kilograms divided by square height in metres). The presence or absence of diabetes was recorded based on the history

provided by the participant. Participants who consumed alcohol, smoked, and chewed tobacco were termed as alcohol consumers, smokers, and tobacco chewers respectively, while those who did not during their lifetime until the day of examination were defined as non-alcohol consumers, non-smokers and non-tobacco chewers.

The distant visual acuity was measured and recorded by Log Mar tumbling E charts. Blindness was graded according to ICD 10th edition. Objective refraction was done using a streak retinoscope (Beta 200 Heine, Germany) followed by a subjective refraction. A detailed ocular examination was performed with a slit lamp biomicroscope (BD 900, Haag-Streit International, Bern, Switzerland). This included measurement of IOP by Goldmann applanation tonometer (AT900, Haag-Streit International), Van Herrick's method for grading of peripheral anterior chamber depth followed by gonioscopy using a 4-mirror gonioscope (Carl Zeiss AG, Oberkochen, Germany). The angle was graded according to the Shafer's grading system. All participants underwent anterior segment photography. Anterior segment optical coherence tomography (OCT, Topcon 3D OCT 2000) was used for measuring central corneal thickness (CCT), iris thickness, and ACA width. The ACA width was measured in degrees using calipers. The AL, lens thickness, keratometry (CCR horizontal and vertical) and ACD were measured by ocular biometry (Nidek A scan, Optical Biometer) in all participants. Those participants with cataracts were graded in accordance with the Lens Opacities Classification System (LOCS) III (Chyalack et al., 1993). All participants underwent automated visual field test (SITA Standard 24-2 program HFA II 745i, Carl Zeiss, India), fundus photography, and posterior segment OCT. Stereoscopic fundus examination was done using 90-dioptre lens (Volk Optical Inc., Mentor, OH, USA) and when required indirect ophthalmoscopy was performed using 20-dioptre lens. Vertical cup disc ratio (VCDR) was measured with an eye piece graticule and recorded in units of 0.05 (Haag-Streit International). The criteria for diagnosing POAG was according to the International Society for Geographical and Epidemiological Ophthalmology (ISGEO) definition.

This study was approved by the Ethical Review Board of Nepal Health Research Council (Reference number: 622) and Institutional Review Committee of Tilganga Institute of Ophthalmology and was in accordance to the tenets of the Declaration of Helsinki.

Data were recorded and coding was done for each parameter and entered into Microsoft (MS) Excel Shet. Data were managed by using MS Excel. Statistical analysis was done by IBM SPSS Statistics version 19 (IBM Corp., Armonk, N.Y., USA). Chi-square test was used to test the significance of relationship between two variables. Correlation between the two variables was done by using Pearson correlation coefficient and Spearman coefficient where appropriate. Results were taken out as odds ratios (OR) with their 95% confidence interval (CI) for their association with each determinant with POAG. A bivariate analysis was done followed by a multiple regression analysis when required to study the association of possible determinants with POAG.



# **RESULT**

The overall prevalence of POAG was 1.81% among the total 2042 participants above the age of 18 years, 2.53% in 30 years and above and 3.41% in 40 years and above (Table 1). There was an increase in the prevalence after the age of 40 years and the highest was noted in the age group of 70 years to 79 years. The overall prevalence of POAG in males and females was 0.98% and 0.83% respectively.

There were 37 cases with POAG and 148 controls. In 34 (94.5 %) cases, POAG was seen in both eyes while in three (5.4%) cases only one eye was affected. The difference in IOP and CCT between the right and left eye was not statistically significant hence the left eye was taken for analysis.

The mean age with standard deviation (SD) of participants in cases was  $61.22 \pm 13.15$  years and in control was  $60.16 \pm 13.30$  years. Among the cases, males constituted 20 (54.1%) and females 17 (45.9%), while in the controls, males constituted 80 (54.1%) and females 68 (45.9%).

The demographics, clinical associations and bivariate analysis of cases (POAG) and controls have been tabulated (Tables 1, 2). There were four participants with a family history of glaucoma, of which two (5.4%) were cases and two (1.4%) controls. The number of self-reported HTN among cases and controls was nine (24.3%) and 31 (20.9%) respectively, when the blood pressure (BP) was measured the numbers among cases and controls were 20 (57%) and 73 (52.1%) respectively. There were two (5.4%) participants with DM in cases and five (3.4%) in controls. The mean BMI of cases and control

was  $21.35 \pm 4.40$  and  $21.31 \pm 4.27$  respectively. None of the clinical characteristics (HTN, DM, BMI, smoking, alcohol, and chewing tobacco) showed an association with POAG.

In the ocular parameters, median best corrected visual acuity (BCVA) in cases was 0.2 (range 0 to 2.08) and controls was 0.1 (range 0 to 3.7) (p = 0.823). The mean IOP was  $15.34 \pm 3.74$  in cases and  $13.72 \pm 2.54$  in controls (P = 0.019). The mean CCT was  $515.71 \pm 41.14$  in cases and  $522.01 \pm 41.09$  controls (P = 0.447). The mean ACA was significantly higher in cases (37.56  $\pm$  9.43) than in the controls (32.30  $\pm$  8.59) (P = 0.004). The vCDR was significantly higher (p < 0.001) in cases  $0.6 \pm 0.25$  (range 0-0.90) than controls  $0.31 \pm 0.1$  (range 0-0.70). Retinal nerve fibre layer (RNFL) was also significantly thinner in cases  $87.68 \pm 14.43$  than controls  $103.34 \pm 15.21$ , (P < 0.000), while the thickness of macula did not differ much between the groups, cases  $(265.2 \pm 21.5)$  and controls (268.4) $\pm$  17.4) (p = 0.41). Similarly, the median of mean deviation (MD) and pattern standard deviation (PSD) in visual field was significantly higher in cases -5.81 (range -20.19 to -0.48) and 6.19 (range 1.67 to 13.08) (P = 0.020) as compared to controls -3.39 (range 19.40 to 7.32) and 2.17 (range 0.89 to 13.59) (p < 0.001) respectively. The bivariate analysis showed that there was association of POAG with a higher IOP, wider ACA, larger vCDR, thinner RNFL, and worse mean and pattern standard deviation. Other factors such as BMI, DM, HTN, family history of glaucoma, smoking, alcohol consumption, tobacco chewing, refractive error, CCT, CCR, ACD, AL, lens thickness, and iris thickness were not associated.

The results of bivariate and multivariate analysis were similar showing the persistent effects of high IOP, wide ACA, large vertical cupping, thinner RNFL, and worse visual field global indices, indicating strong association with POAG (Table 3).

The correlation between different variables in the POAG group have been tabulated (Table 4). There was a weak correlation between IOP and CCR (Pearson coefficient for horizontal r 0.396 and for vertical 0.332), similarly CCT had a positive correlation with CCR (Pearson coefficient for horizontal r 0.605 and for vertical 0.544). The RNFL negatively correlated with PSD (Spearman correlation r -0.507) while macular thickness positively correlated with MD (Spearman correlation r 0.454). There was no correlation between IOP and CCT.

Table 1: Demographics, clinical characteristics and bivariate analysis of cases of primary open-angle glaucoma and controls.

Variables	Case Control		n valua	Bivariate analysis	
variables	Mean ±SD	Mean ±SD p-val		95% CI	OR
Mean Age (years)	$61.22 \pm 13.15$	$60.16 \pm 13.30$	0.664		
Male, n (%)	20 (54.1%)	80 (54.1%)	1		
Female, n (%)	17 (45.9%)	68 (45.9%)	1		
Family history glaucoma (Yes)	2 (5.40%)	2 (1.35%)	0.212		
BMI (Mean ± SD)	$21.35 \pm 4.40$	$22.31 \pm 4.27$	0.226	0.86-1.04	0.94
HTN (Questionnaire), n (%)	9 (24.3%)	31 (20.9%)	0.66	0.52-2.83	1.21
HTN (Measurement), n (%)	20 (57%)	73 (52.1%)		0.54-2.31	1.12
Diabetes (Yes), n (%)	2 (5.4%)	5 (3.4%)	0.63	0.30-8.78	1.63
Smoking (Yes), n (%)	15 (40.5%)	40 (27%)	0.4	0.64-3.2	1.42
Alcohol (Yes), n (%)	21 (56.8%)	91 (61.5%)	0.14	0.72-8.84	2.53
Chewing tobacco (Yes), n (%)	6 1 (6.2%)	31 (20.9%)	0.87	0.40-2.15	0.93

Table 2: Ocular characteristics and bivariate analysis of cases of primary open-angle glaucoma and controls.

Variables	Case mean±SD	Control mean±SD	p-value	95% CI	OR
BCVA, Median	0.2	0.1	0.823	0.98-4.63	2.13
(Range)	(range 0 to 2.08)	(range 0 to 3.7)	0.023	0.76-4.03	2.13
IOP	$15.34 \pm 3.74$	$13.72 \pm 2.54$	0.019	1.06-1.36	1.20
CCT	515.71 ±41.14	$522.01 \pm 41.09$	0.447	0.99-1.01	0.996
CCRv	$7.1 \pm 1.2$	$6.86 \pm 1.4$	0.343	0.85-1.58	1.16
CCRh	$6.93 \pm 1.01$	$6.64 \pm 1.5$	0.961	0.87-1.14	0.997
ACD	$3.24 \pm 0.42$	$3.17 \pm 0.32$	0.287	0.60-5.68	1.85
ACangle	$37.56 \pm 9.43$	$32.30 \pm 8.59$	0.004	1.02-1.12	1.07
Axial Length	$23.14 \pm 0.81$	$22.87 \pm 0.92$	0.121	0.91-2.21	1.42
Iris thickness	$438.67 \pm 61.69$	$447.17 \pm 46.5$	0.404	0.99-1.01	1.00
Lens thickness	$3.74 \pm 0.57$	$3.67 \pm 0.56$	0.503	0.63-2.58	1.27
vCDR	$0.6 \pm 0.25$	$0.31 \pm 0.15$	< 0.001	1.72-2.83*	2.10*
hCDR	$0.52 \pm 0.23$	$0.30 \pm 0.15$	< 0.001	1.7-2.8*	2.16*
RNFLtotal	$87.68 \pm 14.43$	$103.34 \pm 15.21$	< 0.001	0.91-0.97	0.94
Macular thickness	$265.2 \pm 21.5$	$268.4 \pm 17.4$	0.41	0.91#	0.72-1.15#
MD, Median (Range)	-5.81 (range -20.19 to 0.48)	-3.39 (range-19.40 to 7.32)	0.020	0.83-0.98	0.9
PSD, Median (Range)	6.19	2.17	< 0.001	1.096-1.42	1.25
	(range 1.67 to 13.08)	(range 0.89 to 13.59)	\0.001	1.070-1.72	1.23
Emmetropia, n (%)	27 (73%)	100 (67.6%)			
Hypermetropia, n (%)	2 (5.4%)	26 (17.6%)	0.15	0.06-1.28	0.26
Myopia, n (%)	8 (21.6%)	22 (14.9%)		0.54-3.36	1.35

<sup>\*</sup>adjusted OR for 0.1-unit increment, # Adjusted OR for 10-unit increment

Table 3: Multivariate analysis of 37 cases of primary open-angle glaucoma and 148 controls.

Variables	OR	95% CI	p-value
IOP	0.96	0.77-1.2	0.74
vCDR	1.62*	1.13-2.32*	0.01
RNFLtotal	0.96	0.92-1.01	0.09
ACangle	1.15	1.11-1.26	0.01
MD	1.01	0.85-1.21	0.89
PSD	1.14	0.88-1.49	0.33

<sup>\*</sup>adjusted for 0.1-unit increment

Table 4: Correlation of different variables with primary open-angle glaucoma.

Variables	Correlation coefficient (r)	p-value
IOP and CCRv	0.396	0.034
IOP and CCRh	0.332	0.051
CCT and CCRh	0.605	0.000
CCT and CRv	0.544	0.002
vCDR and RNFL	-0.576	0.001
RNFL and PSD	-0.507	0.014
Macular thickness and MD	0.454	0.026

# **DISCUSSION**

The prevalence of POAG was 3.4% in participants above the age of 40 years, which was 2.7 times higher than a large population based study conducted in Bhaktapur district of Nepal (1.24%) (Thapa et al., 2012a). The prevalence of POAG was also higher than population-based studies conducted in South Asia (Casson et al., 2007; Dandona et al., 2001). The reason for a higher prevalence of POAG in our study could have been due to our study population, which comprised of a large family belonging to one pedigree. A genetic analysis of this study population will be necessary to comment further on the above statement.

An increase in age was associated with a higher prevalence of POAG, which is an established associated factor for developing glaucoma (Dandona et al., 2001; Vijaya et al., 2008). The prevalence of POAG was higher in males than females, which is similar to results from Leske (2009) study.

There are varied results showing the association between BMI and POAG. Several studies have shown association between high (Kaimbo et al., 2001) and low (Yan et al., 2015) BMI with POAG, while some have shown that there is no relation between the two (Suzuki et al., 2006). In this study there was no difference in BMI among the case and control groups. The possible reason could be that individuals participating in this study belonged to a single extended pedigree containing >62,000 pairwise relationships, leading to a very low gene flow (< 1% per generation) into the population from other ethnic groups (Williams-Blangero et al., 1990). The BMI and POAG were weakly correlated in present study.

There were only two participants with a family history of POAG in both the groups. There was no association between family history and glaucoma which could be because of the lack of awareness of the disease. It has been well documented from a large population based study conducted in Nepal, that more than 90% of an urban population was unaware of glaucoma (Thapa et al., 2011).

The relationship between the level of BP and glaucomatous damage is still unclear. Any

vascular dysregulation due to high or low BP can cause decrease in ocular perfusion, which may be an underlying cause for glaucoma (Leske, 2009). Both high and low BP has been associated with POAG (Quigley, 1996). There are studies where HTN is positively associated (Mitchell et al., 2004) and not associated with POAG (Kaimbo et al., 2001). In present study HTN was not associated with POAG. The authors are unable to comment on the role of DM as a contributing factor for POAG because the patients who were classified as diabetics were self-reported (through questionnaire).

Current study did not show any association of smoking or chewing tobacco and alcohol consumption with POAG. The association between tobacco smoking and glaucoma in various studies has shown controversial results (Klein et al., 1993). A prospective follow-up study showed that neither current nor former smokers were at risk of developing POAG than those who had never smoked, and that heavy smoking did not seem to increase the risk of POAG (Klein et al., 1993). A meta-analysis showed that smokers (current and former) had a higher mean IOP than non-smokers and that current smokers had an increased risk of POAG when compared to former and any smokers (Rong et al., 2016). A study conducted in India showed chewing tobacco as a positive risk factor for POAG while alcohol intake was not found to be a risk factor (Garg et al., 2014). Another study showed positive association between high alcohol consumption and POAG (Al Owaifeer et al., 2018). There are studies reporting that alcohol intake has a role on the optic nerve head blood perfusion resulting in a protective effect against glaucoma (Al Owaifeer et al, 2018).

The 97.5th and 99th percentiles of IOP in the control group were 20 and 20.5 mmhg respectively. The mean IOP was significantly higher in the POAG group when compared to the control group. A one -time measurement of the IOP could have led to an underestimation of the IOP measurement resulting in a greater number of participants with NTG within the POAG group as compared to the HTG group 10 (37.8%). The Bhaktapur Glaucoma Study has also reported IOP within the normal range in those who had POAG. There are also other studies from the region which have reported the same (Kim et al., 2011, Thapa et al., 2012a). Although the IOP has not been recommended as a screening parameter for the diagnosis of POAG, the level of IOP however is an important risk factor (Vijaya et al., 2008). The mean vCDR in the control was 0.3 the 97.5th percentile and 99th percentile of vCDR was 0.6 and 0.7 respectively, while the mean vCDR was 0.6 in the POAG group. Several studies have reported that with an increase in the vCDR, the chances of developing glaucomatous damage was higher (Gordon et al., 2002; Iester et al., Mean total RNFL was significantly thinner in the POAG group than the control group but was not found to be a risk factor for POAG.

VF was done on all the participants but only 66.7% reports were reliable for interpretation. An increase in the MD and PSD was associated with an increased risk of developing glaucoma. There was a negative correlation between RNFL thickness and PSD and a weak correlation of macular thickness and MD. A similar correlation of the RNFL thickness and macular thickness with MD and PSD in POAG patients have been reported in other studies (Dagdelen et

al., 2018). Macular thinning as one of the early glaucomatous changes has also been reported (Iester et al., 2012).

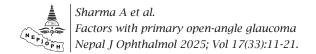
The difference in CCT between the two groups was not statistically significant. Studies have shown no differences in the CCT between POAG and normal population (Vijaya et al., 2008), while others have reported a thinner CCT in those with POAG (Aghaian et al., 2004). The mean CCT in this population was thinner than the mean CCT reported in another population based study done in Nepal (Thapa et al., 2012b). The reason for the difference between these two study populations could be attributed to the homogenous population in our study, environmental and genetic factors (Vijaya et al., 2008). Similarly, racial differences in CCT have been reported through several populations based studies (Toh et al., 2005) which could have played a role as well. Unlike many other studies, CCT and IOP did not show a correlation (Ehlers et al., 1975). Hence, measurements of IOP may not be influenced by the CCT in this population.

CCR becomes steeper and CCT thinner with age due to physiological changes that alter the elasticity of the cornea and decrease the number of keratocytes (Aghaian et al., 2004, Ehlers et al., 1975). There was a weak correlation between the CCRh and CCT. Some have found a negative correlation between the two (Shimmyo et al., 2003) while others have shown no correlation (Chen et al., 2009). There are only a few studies that have shown an association of CCR and POAG while most others have shown no association (Ehlers et al., 1975). Similarly, CCR and IOP were also positively correlated.

The iris was thinner, AC deeper, AC angle was wider and axial length was longer in the POAG group. The differences however did not reach statistical significance but is an interesting finding. We are unable to explain the reason why the mean ACA was significantly wider in the POAG group. Comparisons of mean ACD should be made carefully, as significant differences between groups regarding age and refractive error may influence the findings. It has been reported that a wide ACA was associated with a deeper ACD, longer AL, higher corneal power, and IOP (Schuster et al., 2016).

There was no difference in the BCVA between the two groups. Refractive error was not associated with POAG. A large majority of the study population were emmetropic which could have led to the above finding. Although there is an association of myopia with glaucoma (Mitchell et al., 2004) there have been reports that have shown no association between the two (Vijaya et al., 2008). The OHTS (Gordon et al., 2002) and the EMGT also did not find a higher incidence or progression of POAG in myopic individuals. Majority of POAG participants. had visual field defects that did not affect the central field of vision

There were several strengths to this study: It was a population based oculo-genetic study conducted in a single pedigree, glaucoma was diagnosed by the ISGEO criteria and ocular examination was done by one glaucoma specialist. The limitations of the study were that, some of the data were incomplete for various reasons such as unwillingness, uncooperativeness to undergo examination and media haze which prevented examination. The other limitation was that



the diagnosis of diabetes was based upon the questionnaire and not the blood sugar level.

# **CONCLUSION**

To summarize there are several factors associated with POAG. There was an established association of IOP, ACA, CDR, NFL thinning, MD and PSD, while there was no association of BMI, DM, HTN, smoking, chewing tobacco, alcohol consumption, CCT, CCR, ACD, iris thickness, lens thickness, axial length and

macular thickness with POAG. Awareness programs and screening strategies have to be developed and implemented for a targeted population such as those above the age of 40 years, elevated IOP, large vertical disc cupping, thin RNFL and worse global indices on visual field tests to prevent irreversible blindness due to glaucoma.



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