



## Original Research Article

## Association of risk factors with the severity of primary open angle glaucoma

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## ABSTRACT

**Aim:** To study the associations of risk factors with the severity of primary open angle glaucoma.**Materials and Methods:** A total of 98 patients were enrolled in the study as per the inclusion criteria. A complete ophthalmologic examination including a medical history review, best-corrected visual acuity, slit lamp examination and visual field assessment with Carl Zeiss Perimeter was done.**Results:** 98 patients were studied. The mean age of the patients was  $60 \pm 10.3$  years. There were 49% males and 51% females. Out of the participants, 22% had mild glaucoma, 37% had moderate glaucoma and 41% had severe glaucoma. Age was associated with 56% increase in likelihood of severe glaucoma per decade compared to mild disease. Myopia was seen in 60% of patients from the severe glaucoma group. Hypertension was seen in 49% of the participants. Diabetes was seen in 27%. Family history of 7% was noted. Hypothyroid was seen in 6% of the patients.**Conclusion:** In our study, we found that advancing age; myopia; hypertension and hypothyroid had a correlation with POAG. However, the association of diabetes with POAG did not have a reliable conclusion.© 2020 Published by Innovative Publication. This is an open access article under the CC BY-NC-ND license (<https://creativecommons.org/licenses/by/4.0/>)

## 1. Introduction

Glaucoma is the second most common cause of blindness as accounted from the blindness certification.<sup>1</sup> It is a leading cause of Global irreversible blindness. POAG is the most common form of glaucoma & affects 44.1 million individuals worldwide.<sup>2</sup>

Primary open-angle glaucoma (POAG) is a chronic, progressive optic neuropathy in adults in which there is a characteristic acquired atrophy of the optic nerve and loss of retinal ganglion cells and their axons. This condition is associated with an open anterior chamber by gonioscopy.<sup>3</sup> Multiple literature review studies suggest that there are a number of risk factors associated with POAG like Race, Family history, Older Age, Higher IOP, Myopia, Type 2 Diabetes Mellitus and Hypertension.

In this article, we report the association of the risk factor with the severity of POAG from the patients seen in our glaucoma clinic at DY Patil Hospital.

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## 2. Materials and Methods

This study was performed with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

In this prospective study, we included 98 patients from our glaucoma outpatient clinic conducted at the Ophthalmology department at Dr. D.Y. Patil Hospital, Mumbai.

All patients who were enrolled in the study underwent complete ophthalmological examination. Visual acuity was recorded with the Snellens chart for distant and near vision.

Slit lamp biomicroscopy was performed by our glaucoma specialist to identify abnormalities of the anterior segment. Under topical anesthesia using 0.5% proparacaine, intraocular pressure was measured with Applanation Goldman Tonometry using 0.5% proparacaine and fluorescein staining of the tear film.

Gonioscopy was performed on all subjects with a two mirror Zeiss lens in dim ambient illumination with a small slit that does not fall on the pupil. The angle was graded

according to the Shaffers system as follows. All open angle glaucoma patients were then selected.

30-2 Perimetry scan was then done to analyse the visual fields.

Dilatation of the patient was carried out using 1% tropicamide plus 2.5% phenylephrine. Once the patient was dilated, a stereoscopic evaluation for the optic nerve head was performed using a +90 diopter lens. Along with the cup:disc margins and ratio, presence of any notching, splinter haemorrhages, and peripapillary atrophy were documented.

The inclusion parameters in this study were:

1. Elevated Intraocular Pressure > 21mm/Hg without any treatment at 2 occasions
2. Wide and Open angles on Gonioscopy
3. Corrected visual acuity 20/200 or better
4. Typical optic disc changes showing diffuse or localized rim thinning with Neuro-retinal rim loss, enlarged cupping, peri-papillary atrophy, notching and disc hemorrhage (may or not be present), asymmetry in cup/disc ratio of >0.2 between the two eyes.
5. ISGEO Classification:<sup>4</sup>

Category 1 (Structural & Functional Evidence): Eyes with a CDR or CDR asymmetry  $\geq$  97.5th percentile for the normal population, or a neuroretinal rim width reduced to  $\leq$  0.1 CDR (between 11 to 1 o'clock or 5 to 7 o'clock) that also showed a definite visual field defect consistent with glaucoma.

Category 2 (Advanced Structural damage with Unproved Field Loss) : If the subject could not satisfactorily complete visual field testing but had a CDR or CDR asymmetry  $\geq$  99.5th percentile for the normal population, glaucoma was diagnosed solely on the structural evidence.

Category 3 (Optic Disc Not Seen, Field test Impossible): If it is not possible to examine the optic disc, glaucoma is diagnosed if: (A) The visual acuity <3/60 and the IOP >99.5th percentile, or (B) The visual acuity <3/60 and the eye shows evidence of glaucoma filtering surgery, or medical records were available confirming glaucomatous visual morbidity

The exclusion parameters in this study were:

1. History of any intraocular surgery in normal and suspect groups (except uncomplicated cataract and trabeculectomy)
2. History of previous angle closure attack
3. Secondary causes of elevated IOP (pseudo-exfoliation syndrome, Pigment dispersion, corticosteroid use, iridocyclitis, trauma, other intraocular disease)
4. Disease affecting vision (pituitary lesions, demyelinating diseases, HIV, Acquired immunodeficiency syndrome)

5. Diseases affecting colour vision
6. Any disc anomaly
7. Patient suffering from neurological disorder affecting visual field
8. Any pathological changes in the posterior segment.
9. Visual fields False Positive responses, false negative responses or fixation losses more than 33% were considered unreliable

Anderson's criteria for the diagnosis of glaucomatous visual field defect was defined as:

1. A cluster of 3 or more non edge points in a location typical for glaucoma all of which are depressed on the pattern deviation plot at  $p < 5\%$  level and one of which is at  $p < 1\%$  level on 2 consecutive fields
2. A corrected pattern standard deviation (CPSD) or pattern standard deviation (PSD) (in SITA) that occurs in less than 5% of normal fields on 2 consecutive fields
3. A Glaucoma Hemifield Test outside normal limits on 2 consecutive fields.

We classified the severity of glaucoma based on the criterion outlined below:

### 2.1. Mild glaucoma

1. Definite optic disc or RNFL abnormalities consistent with glaucoma.
2. Normal glaucomatous visual field as tested with SAP.
3. Mean deviation no worse than -6dB.

### 2.2. Moderate glaucoma

1. Definite optic disc or RNFL abnormalities consistent with glaucoma.
2. Glaucomatous visual field abnormalities in one hemifield that are not within 5 degrees of fixation as tested with SAP.
3. Mean deviation worse than -6dB, but no worse than -12dB.

### 2.3. Severe glaucoma

1. Definite optic disc or RNFL abnormalities consistent with glaucoma.
2. Glaucomatous visual field abnormalities in both hemifields and /or loss within 5 degrees of fixation as tested with SAP.
3. Mean deviation worse than -12dB.

## 3. Results

Continuous variables were expressed as mean with standard deviation or median with interquartile range (IQR) while categorical variables were expressed as proportions. For analytic statistics, the worse eye was defined as the eye

with the more severe stage of glaucoma. If both eyes had the same stage of glaucoma, the right eye was considered as the worse eye. Similarly, BCVA was converted into the logarithm of minimal angle of resolution (logMAR) for analysis. The IOP and BCVA of the worse eye were defined based on whether the right or left eye was the eye with the worse stage of glaucoma.

Group wise comparisons for continuous variables were made using the student t test or Wilcoxon ranksum test for nonparametric variables. Analysis of variance (ANOVA) or the Kruskal Wallis test was used to compare variables across the three groups with mild, moderate or severe glaucoma. The chi square test or Fisher's exact test was used to analyse group differences across categorical variables. A univariate and multivariate ordinal logistic regression analysis was carried out to determine the risk factors for moderate and severe glaucoma compared to mild glaucoma. The covariates used in the multivariable ordinal regression models were based on  $p < 0.1$  in univariate models of evidence from literature of the influence of the covariate on the severity of glaucoma. The outcomes were expressed as odds ratios (OR) with 95% confidence intervals (CI) and p values.

All data was entered in MS Excel and was analysed using STATA 12.1 I/c (STATA Corp, Fort Worth, Texas, USA) statistical analysis software package. All p values less than 0.05 were considered statistically significant.

We included 98 patients with different severity of glaucoma during the study period. As per definitions described above, 22 patients (22%) had mild glaucoma, 36 had moderate glaucoma (37%) and 40 had severe glaucoma (41%).

The mean age of patients was  $60.5 \pm 10.3$  years (median= 60 years, Interquartile range= 55 – 68 years, range = 35 – 82 years). The age distribution across the study group and various stages of glaucoma is shown in Figure 1

There were 48 men (49%) and 50 women (51%) in the study.

The mean age of men was  $60.9 \pm 7.7$  years and that of women was  $60.1 \pm 12.4$  years. There was no statistically significant difference in the age of men and women in the study ( $p=0.67$ ).

### 3.1. Systemic risk factors

#### 3.1.1. Hypertension

Hypertension was seen in 48 patients (49%) in the study. There was no difference in proportion of patients with hypertension in those with mild ( $n=12$ , 54%), moderate ( $n=18$ , 50%) or severe glaucoma ( $n=18$ , 45%) (0.17). Distribution of hypertension is shown with respect to glaucoma severity in Figure 2.

#### 3.1.2. Diabetes Mellitus

Diabetes was seen in 26 participants (27%). There were significantly more participants with diabetes in the group with mild glaucoma ( $n=12$ , 54%), compared to moderate ( $n=6$ , 17%) and severe glaucoma ( $n=8$ , 20%) ( $p=0.003$ ). Distribution of diabetes is shown with respect to glaucoma severity in Figure 3.

3.1.2.1. Other systemic diseases. Hypothyroidism was seen in 6 patients (6%), while two patients each had asthma, tuberculosis and history of smoking tobacco. Another 4 (4%) had migraine and 2 had cardiovascular disease.

3.1.2.2. Status of glaucoma – Right and left eye. The mean IOP in the right eye of participants was  $19.7 \pm 4.5$  mmHg (median= 18mm Hg, IQR = 18 – 22mm Hg) and the mean BCVA was  $0.4 \pm 0.5$  logMAR units (median= 0.2, IQR = 0 – 1 logMAR).

Similarly, the mean IOP in the left eye of participants was  $19.6 \pm 5.1$  mmHg (median= 18mm Hg, IQR = 16 – 22mm Hg) mmHg and the mean BCVA was  $0.4 \pm 0.4$  logMAR units (median= 0.2, IQR = 0 – 0.8 logMAR).

There was no difference in the mean IOP ( $p=0.49$ ) and BCVA ( $p=0.31$ ) between the right and left eyes

3.1.2.3. Status of glaucoma – Worse eye. In order to analyse the influence of systemic risk factors on the severity of glaucoma, the worse eye was identified in each patient. As per definitions stated above, the right eye was considered for analysis in 86 participants (88%) and left eye in 12 participants (12%) as it had more severe glaucoma diagnosis.

Table 1 shows a comparison of demographics, systemic and ophthalmic factors across the three stages of glaucoma severity.

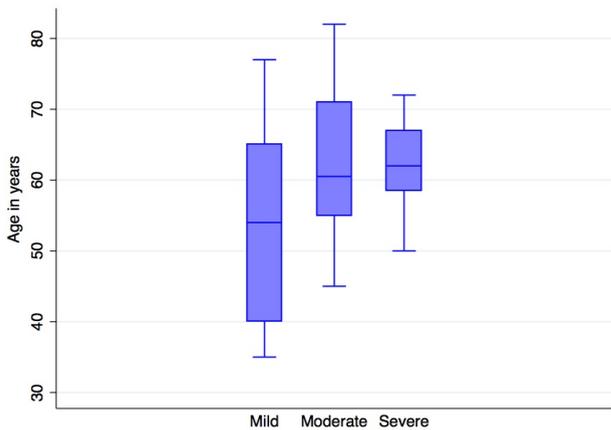
As seen from the table, patients with mild glaucoma were significantly younger (by a mean of 7 years), had significantly more diabetes and migraine and their mean IOP was significantly lower than those with moderate and severe glaucoma. There were no differences in proportion of patients with hypertension and hypothyroidism. Similarly, there was no statistically significant difference in the refractive error and the mean BCVA between these groups.

3.1.2.4. Risk factor assessment – ordinal regression analysis. Since the outcome measure was severity of glaucoma, classified as mild, moderate and severe stages, ordinal regression was performed to assess the odds for developing moderate and severe glaucoma compared to mild glaucoma.

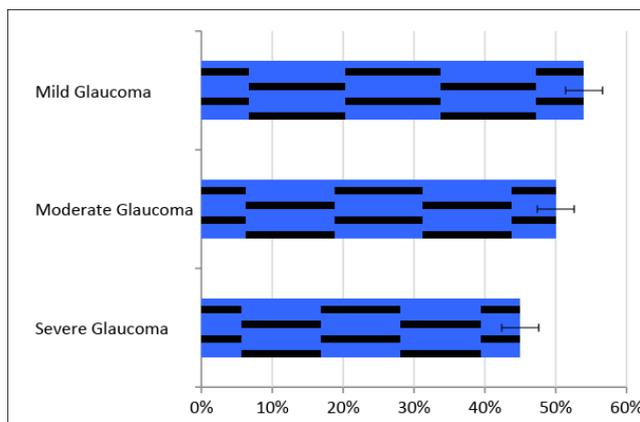
On univariate ordinal regression (Table 2), older age, having hypothyroidism and myopic refraction were associated with higher likelihood of having severe glaucoma compared to mild glaucoma. Similarly, higher IOP and lower BCVA were associated with more severe glaucoma, though these relations were not statistically

significant. However, having diabetes significantly lowered the likelihood of having severe glaucoma.

On multivariable ordinal regression, every 10-year increase in age was associated with a 56% increase in likelihood of greater severity of glaucoma compared to mild disease ( $p=0.02$ ). Similar to the univariate analysis, having diabetes significantly lowered the likelihood of having severe glaucoma, and the risk reduced by 66% (95% CI ranged between 16% - 87% lower risk) compared to those with mild glaucoma (Table 2).



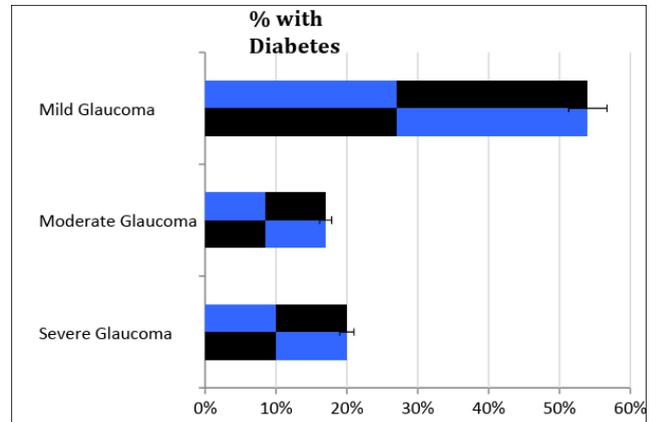
**Fig. 1:** Box and whisker plot showing distribution of age of participants in the study with respect to severity of glaucoma in the worse eye



**Fig. 2:** Bar diagram with standard error showing distribution of hypertension in the three groups with mild, moderate and severe glaucoma.

#### 4. Discussion

In our cross sectional study involving ninety-eight glaucoma patients, we found that those with mild glaucoma were significantly younger than those with moderate and severe



**Fig. 3:** Bar diagram with standard error showing distribution of diabetes in the three groups with mild, moderate and severe glaucoma

glaucoma and that age was associated with 56% increase in likelihood of severe glaucoma per decade compared to mild disease. Our data also shows that diabetes has a protective effect on the risk of progression to severe glaucoma, even after adjusting for age and other covariates and this risk was 66% lower in multivariable regression models. Though hypertension was found to lower risk of glaucoma severity by 25% in univariate models, this relationship did not attain statistical significance in multivariable models. Similarly, though myopia was found to increase risk of severe glaucoma in univariate models, this relationship did not sustain statistical significance in multivariable models.

Age has been shown to be associated with increase severity of glaucoma in many previous studies. The cup to disc ratio increases and visual field show corresponding and progressive constriction with increase in the duration of glaucoma. In a large study enrolling 587 patients, De Moraes et al showed that, increasing age was associated with 19% increase in severity of glaucoma per decade of life.<sup>5</sup> Authors also showed that in multivariable model, peak IOP, thinner central corneal thickness, optic disc haemorrhage, and presence of beta-zone para papillary atrophy were other factors associated with progression of visual fields and glaucoma severity. Recently, Jonas et al reviewed the world literature on glaucoma prevalence and reported that increasing age, high myopia, sub-Saharan African ethnicity and a positive family history were the most common risk factors for onset and progression of open angle glaucoma.<sup>6</sup> They also found that older age. Asian ethnicity and hyperopia were risk factors for angle closure glaucoma. This very large study clearly shows that older age was associated with greater risk of glaucoma progression, irrespective of type of glaucoma. In another study, Kostanyan et al showed that older age is associated with increase structural and functional glaucoma progression from a large cohort of patients with American and Korean

**Table 1:** Comparison of demographics, systemic and ophthalmic factors across the three stages of glaucoma severity.

Variable	Mild glaucoma (n=22)	Moderate Glaucoma (n=36)	Severe Glaucoma (n=40)	P value
Age (years)	55 + 13.2	62.2 + 11.1	62.05 + 6.0	<b>0.01</b>
Gender (% Men)	10 (45%)	14 (39%)	24 (60%)	0.17
Hypertension (n, %)	12 (54%)	18 (50%)	18 (45%)	0.76
Diabetes (n, %)	12 (54%)	6 (17%)	8 (20%)	<b>0.03</b>
Hypothyroidism	2 (9%)	4 (11%)	0	0.09
Migraine	4 (18%)	0	0	<b>&lt;0.001</b>
Mean IOP (mmHg)	17.4 + 3.5	20.5 + 6.2	21.3 + 4.8	<b>0.002</b>
Mean BCVA (logMAR)	0.34 + 0.44	0.45 + 0.48	0.48 + 0.51	0.63
Refractive error (%myopia)	8 (36%)	14 (39%)	24 (60%)	0.11

**Table 2:** Univariate and Multivariable ordinal regression analysis to determine risk factors for severity of glaucoma stage.

Variable	Interval	Univariate analysis		Multivariable analysis		
		Odds ratio	95% CI	Odds ratio	95% CI	P value
Age	10 year increment	1.49**	1.04 - 2.2	1.56**	1.07 - 2.27	0.020
Gender	Female vs. Male	0.57	0.27 - 1.2	—	—	—
Hypertension	Vs. no hypertension	0.75	0.36 - 1.6	0.98	0.46 - 2.1	0.97
Diabetes	Vs. no diabetes	0.32**	0.13 - 0.8	0.34**	0.13 - 0.84	0.019
Hypothyroidism	Vs. no Hypothyroidism	1.11	0.7 - 1.7	—	—	—
IOP	1 mmHg increment	1.06	0.9 - 1.2	—	—	—
BCVA	1 line decrement	1.02	0.5 - 2.2	—	—	—
Myopia	Vs. hyperopia	2.19**	1.02 - 4.6	1.95	0.89 - 4.25	0.09

\*\*p&lt;0.05

descent.<sup>7</sup>

In another study, Yu et al prospectively assessed the risk of visual field progression over a 5-year period in glaucoma patients with progressive retinal nerve fibre layer thinning and found that increasing age was associated with greater severity of glaucoma.<sup>8</sup> Authors performed serial retinal nerve fiber layer assessment on 240 eyes with glaucoma and proved that detecting progressive RNFL thinning should be central to initiate or augment treatment for glaucoma patients. Age can be considered as a surrogate for the duration of glaucoma and those who live longer with glaucoma are prone to have more severe disease, even with control of IOP. Several mechanisms may be related to greater severity of glaucoma and increasing age. Longer duration of oxidative damage, longer exposure to increased IOP with structural damage at the lamina cribrosa and progressively greater trabecular outflow obstruction may be some of the reasons that those with greater age and longer duration of glaucoma have more severe glaucoma.<sup>9,10</sup> In angle closure disease, there may be slightly different mechanisms involved for increasing glaucoma severity with increasing age. These eyes experience progressive narrowing of the anterior chamber angle with age predominantly due to increase in the thickness of the lens and greater lens vault pushing the iris diaphragm forward, leading to a shallow the anterior chamber

and crowding of the anterior chamber angle.<sup>11-13</sup> This mechanism has been shown to be especially true in Asian eyes.<sup>6,7,14</sup> Due to this mechanism, many advocate early cataract surgery in patients with angle closure<sup>15-17</sup> and some even recommend clear lens extraction to alleviate the risk of glaucoma and its progression.<sup>18-20</sup>

In our study we found 60% myopic patients with severe glaucoma in comparison to 39% and 36% for moderate and mild glaucoma respectively. Our study shows results similar to Perera et al, in the Singapore Malays study showed that persons with moderate or high myopia had an 3 times higher risk of POAG when compared to those with emmetropia.<sup>21</sup>

Even though many studies found a correlation with hypothyroidism and glaucoma<sup>22-27</sup> some of the epidemiological study carried out by Motsko et al did not find any association with patients having hypothyroid and glaucoma, our study showed similar results. Out of the 20% who had hypothyroidism, 9% were of the mild glaucoma group and the remaining 11% had moderate glaucoma. We did not notice a significant difference between the occurrence of hypothyroidism and the severity of glaucoma.

The relationship between glaucoma and diabetes has been controversial and the evidence inconclusive over the years with some studies showing increased risk while others claiming reduced risk of glaucoma progression and severity in patients with diabetes. In the ocular hypertension

treatment study (OHTS), a very large multicentric randomised controlled study enrolling more than 1600 American participants with raised IOP without evidence of glaucoma at baseline, a self reported history of diabetes mellitus appeared to be significantly protective against developing open angle glaucoma in both univariate and multivariate models, similar to our results.<sup>28</sup> In the OHTS study, among the 191 participants who reported a history of diabetes at baseline, only 6 (i.e. 3.1%) developed glaucoma compared with 119 (i.e. 8.3%) of 1427 participants who did not report a history of diabetes mellitus. The univariate hazard ratio for diabetes mellitus was 0.40 (95% CI, 0.18-0.92), and the multivariate hazard ratio was 0.37 (95% CI, 0.15-0.90). We report almost identical odds ratio of 0.34 from our multivariable analysis which translates to 66% reduction in the risk of glaucoma severity. Similarly, Gangwani et al reported a very low incidence of only 1.8% glaucoma from a diabetic retinopathy screening program involving 2182 subjects.<sup>29</sup> Authors also reported that normal tension glaucoma variant was the commonest type of glaucoma identified in their cohort. Contrary to these findings, Zhao et al,<sup>30</sup> in a meta-analysis of 47 studies from 16 countries, including nearly 3 million patients, found that diabetes increased the risk of glaucoma by 48% (95% confidence= 29% to 71%). They further evaluated that the risk of glaucoma increased by 5% for each year since diabetes diagnosis. They also found that the pooled average difference in IOP comparing patients with diabetes with those without diabetes was 0.18 mmHg, whereas the pooled average increase in IOP associated with an increase in 10 mg/dl in fasting glucose was 0.09 mmHg. From this exhaustive meta – analysis, authors concluded that diabetes, diabetes duration, and fasting glucose levels were associated with a significantly increased risk of glaucoma, and diabetes and fasting glucose levels were associated with slightly higher IOP. In a population based large study, involving data from the NHANES database, Zhao et al again showed that diabetes was associated with an increased risk of open angle glaucoma in an American population.<sup>31</sup> Another Korean population based survey showed increased risk of diabetics to develop glaucoma.<sup>32</sup> In another dutch population participating in the Rotterdam study, Dielemans et al reported that newly diagnosed diabetics mellitus and high levels of blood glucose were associated with high-tension glaucoma.<sup>33</sup> The mechanism involving raised IOP, glaucoma and diabetes is not well elucidated. However, extensive evidence suggests that diabetes may indeed be associated with an increased risk of glaucoma. Since we enrolled diabetics without diabetic retinopathy and did not confirm the diabetic status and relied on self report, it is possible that relatively smaller cohort of 26 diabetic patients was not a good representation of diabetics in the population. The merits of the study are the relatively good sample size and reliable classification of patients into mild,

moderate and severe glaucoma based on cup disc ratio and visual fields parameters. Recording of systemic parameters of interest, such as diabetes and hypertension, was also adhered to as far as possible. The drawbacks are the lack of longitudinal data on glaucoma progression, though this was limited by time constraints in which the study had to be completed.

In conclusion, we found that advancing age was associated with 56% increase in risk of glaucoma severity progression per decade and patients with diabetes had a 66% lower risk of progression of glaucoma severity. Though statistically significant, the association of diabetes was based on a relatively smaller number of patients and may not be a reliable conclusion. Further studies should evaluate the role of systemic risk factors on glaucoma progression in a prospective study design since most current data are based on cross – sectional study designs like ours.

## 5. Conclusions

Thus in conclusion we found that advancing age, myopia, hypertension, diabetes, family history and hypothyroidism were the risk factors associated with POAG.

On univariate ordinal regression, older age, having hypothyroidism and myopic refraction were associated with higher likelihood of having severe glaucoma compared to mild glaucoma. Similarly, higher IOP and lower BCVA were associated with more severe glaucoma, though these relations were not statistically significant.

In conclusion, we found that advancing age was associated with 56% increase in risk of glaucoma severity progression per decade and patients with diabetes had a 66% lower risk of progression of glaucoma severity. Though statistically significant, the association of diabetes was based on a relatively smaller number of patients and may not be a reliable conclusion. Further studies should evaluate the role of systemic risk factors on glaucoma progression in a prospective study design since most current data are based on cross-sectional study designs like ours.

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None.

## 8. Conflict of Interest

None.

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