

Primary open-angle glaucoma progression depending on clinical indices at presentation

S.Iu. Mogilevskyy¹, Dr Sc (Med), Prof.

S.V. Ziablitsev², Dr Sc (Med), Prof.

L. I. Denisiuk¹, Assistant

¹Ophthalmology Department,
Shupik National Medical Academy
of Postgraduate Education,

²Pathophysiology Department,
Bohomolets National Medical
University

Kyiv, Ukraine

E-mail: sergey.mogilevskyy@gmail.
com

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Background: Given the importance of developing simple and efficient methods for the diagnosis and prognosis of primary open-angle glaucoma (POAG), we have previously proposed an index of progression of glaucoma stage (IPGS).

Purpose: To investigate associations between progression of POAG and clinical indices at presentation.

Materials and Methods: The study group comprised 172 patients (78 men (45%) and 94 (55 %) women; mean age at presentation, 57.3 ± 1.1 years) diagnosed with POAG. POAG stage was graded by the Nesterov and Bunin classification of 1975 well as by the Hodapp classification based on the results of the ophthalmological observation of patients over two years. IPGS was calculated as a percentage ratio of (a) a sum of ranked POAG stages and IOP values (categories of IOP) at baseline and study time points and (b) difference between age and disease duration, expressed in years. Sex, age, duration of disease, stage of POAG at presentation, and category of IOP at presentation (IOP0) were input variables used in multiple logistic regression model building.

Results: The IPGS index clearly represented both the change in POAG stages over time and progression of the disease. Age ($r = -0.468$), disease duration ($r = 0.695$), stage of POAG ($r = +0.805$) and IOP category ($r = +0.735$) correlated more significantly than did other variables with IPGS. Patient sex was not correlated with IPGS ($r = -0.169$; $p = 0.027$). The equation for predicting IPGS estimates based on characteristics at presentation was developed through multiple regression: $IPGS = 35.311 - 0.521 \times A + 2.512 \times D + 3.913 \times S + 4.191 \times C$

where IPGS is index of progression of glaucoma stage; A, patient age; D, disease duration; S, POAG stage; C, IOP category.

In terms of the relative impact of the predictors on the IPGS, IOP category had the strongest influence ($\beta = 4.191 \pm 0.446$), followed by stage of POAG at presentation ($\beta = 3.913 \pm 0.356$); disease duration ($\beta = 2.512 \pm 0.313$) and patient age ($\beta = -0.521 \pm 0.022$). The developed equation is characterized by a significant effect of the combination of independent variables on the dependent variable ($R = +0.965$ ($F = 562.35$, $P < .0001$); adjusted $R^2 = +0.931$).

Conclusion: Amongst predictors, IOP category had the strongest influence, while patient age had the weakest influence on the IPGS. The equation for prediction of IPGS can be proposed as early as at presentation and will allow the clinician to conduct individualized treatment of patients.

Introduction

Primary open-angle glaucoma (POAG) is a severe ocular disorder and a leading global cause of blindness and incapacitation [1-3]. The global number of persons with POAG, estimated at more than 44 million in 2010, is expected to rise to 58.6 million by 2020. In 2014, glaucoma was one of the most common (15%) incapacitating ocular conditions in Ukraine, although the figure was insubstantially lower than the figure of 2013 [4]. This may be due to the fact that, in the recent five years, increased attention has been paid in the local ophthalmological community to the disease, leading to somewhat improved early diagnosis and management of this common pathology. The prevalence of glaucoma in

Ukraine in persons aged 18 or older in 2014 was 601.9 per 100,000 persons, corresponding to 212516 totally [5].

Given the attention of Ukrainian ophthalmological community to the diagnosis and prognosis of the disease in this time of economic hardships in our country, developing simple and conventional criteria which enable the clinician to reliably predict pathologic course is important [6]. We have found previously that index of progression of glaucoma stage (IPGS) can be considered such a criterion [7].

The study **purpose** was to investigate associations between progression of POAG and clinical indices at presentation.

Materials and Methods

The study group comprised 172 patients (78 men (45%) and 94 (55 %) women) diagnosed with POAG, and the control group comprised 98 individuals (46 men (47 %) and 52 women (53 %)) without POAG. The mean age of patients was 57.3 ± 1.1 years at the time of detection of POAG. At baseline, complaints were collected and detailed histories were taken, and patients underwent visual acuity testing, Humphrey perimetry, pneumotonometry, refractometry, biomicroscopy, gonioscopy, ophthalmoscopy and ocular coherence tomography (OCT). POAG stage was graded by the Nesterov and Bunin classification of 1975 [2] as well as by the Hodapp classification based on baseline examination. As per the Hodapp classification, in early, moderate and severe glaucomatous loss, mean deviation (MD) was less than -6 dB (corresponding to the first stage), less than -12 dB (corresponding to the second stage), and greater than -12 dB (corresponding to the third and fourth stages), respectively. The examination above was conducted at baseline, 12 months and 24 months.

For the purpose of generalization of data on changes in POAG stages over two years, patients were ranked by IPGS that was calculated using the equation:

$$\text{IPGS} = \frac{(\text{Stage0} + \text{Stage1} + \text{Stage2}) + (\text{IOP0} + \text{IOP1} + \text{IOP2})}{\text{Age} - \text{DD}} \times 100 \%, \quad (1)$$

where Stage0, Stage1 and Stage2 are stages at baseline, 1 year and 2 years, respectively; IOP0, IOP1 and IOP2 are ranked IOP values (categories of IOP) at baseline, 1 year and 2 years, respectively; and DD is disease duration.

Our index (IPGS) takes into account the patient age and disease duration at baseline, changes to the next stage over time, and IOP values at study time points. The index values are expressed as a percentage. IOP categories were defined as per protocol [2, 8]: normal (category 1, up to 23 mmHg); moderately elevated (category 2, 23 mmHg to 32 mmHg); and elevated (category 3, 33 mmHg and above). An IPGS index of 100% is consistent with a patient of young age (25 years) with stage IV POAG and elevated (category 3) IOP at baseline and over the two year observation period, and a DD of 4 years.

Sex, age, duration of disease, stage of POAG at presentation, and category of IOP at presentation (IOP0) were input variables used in multiple logistic regression model building. Statistical analysis was performed using MedCalc v.15.11.0 (MedCalc Software bvba, 1993–2015).

Results and Discussion

Patient observation over two years revealed an increase in the stage of glaucomatous loss ($p < 0.001$) in eyes of the study. Pairwise comparisons (multiple comparisons of dependent samples [9]) revealed an increase in the

number of eyes with more advanced glaucoma stages at year 1 and year 2 compared with baseline ($p < 0.05$ in both cases) as well as an increase in this index at year 2 compared with year 1 ($p < 0.05$).

Table 1 shows IPGS estimates obtained for different stages of POAG. IPGS estimates statistically significantly increased with an advance in the severity of the pathological process (i.e., advance in the stage of the disease). Dispersion analysis was conducted to evaluate the effect of the index on the distribution of POAG stages at the initial phase of the supervision and revealed that the IPGS estimates clearly depended on the stage of POAG ($p = 0.002$). Therefore, the IPGS index (a) clearly represents both the change in POAG stages over time and progression of the disease, and (b) its use is reasonable for further analysis.

Correlation analysis was conducted to find the variables that significantly correlated with IPGS (Table 2). As age ($r = -0.468$), disease duration ($r = 0.695$), stage of POAG ($r = +0.805$) and IOP category ($r = +0.735$) correlated more significantly than did other variables with IPGS, they were selected as predictors for further analysis. Patient sex was not correlated with IPGS ($r = -0.169$; $p = 0.027$), and was not used for further analysis.

Multiple logistic regression analysis was used to develop an equation for prediction of IPGS based on baseline characteristics; the results of the analysis are presented in Table 3. The regression coefficients (or β coefficients) represent the independent contributions of each independent variable to the prediction of the dependent variable. Their analysis showed that, in terms of the relative impact of the predictors on the IPGS, IOP category had the strongest influence ($\beta = 4.191 \pm 0.446$), followed by stage of POAG at presentation ($\beta = 3.913 \pm 0.356$); disease duration ($\beta = 2.512 \pm 0.313$) and patient age ($\beta = -0.521 \pm 0.022$).

The magnitudes and significance of the estimated regression coefficients of selected predictors are shown in the Pareto chart (Fig. 1). The chart confirms that IOP category has the highest magnitude of effect, whereas patient age has the lowest magnitude of effect in our multiple regression model for predicting IPGS in patients with POAG.

Regression analysis demonstrated a significant effect of the combination of independent variables on the dependent variable ($F = 562.35$, $P < 0.0001$). The R was $+0.965$, indicating that approximately 96.5% of the variance in IPGS was accounted for by the combination of independent variables in the model. In addition, the model fit was excellent (adjusted $R^2 = +0.931$).

Therefore, the obtained results allowed us to present the equation for calculating IPGS in the following way (equation 2):

$$\text{IPGS} = 35.311 - 0.521 \times A + 2.512 \times D + 3.913 \times S + 4.191 \times C, \quad (2),$$

where IPGS is index of progression of glaucoma stage; A, patient age; D, disease duration; S, POAG stage; C, IOP category

Table 4 demonstrates the residuals (predicted with the use of equation (2) minus observed IPGS values). Maximum and minimum residuals of IPGS values did

not exceed +6.52 and -6.85, respectively. The difference between mean IPGS values was not significant ($p = 0.49$). Figure 2 shows the scatter plot of predicted versus observed IPGS for the multiple regression model.

Conclusions

First, correlation and regression analyses demonstrated that, in terms of the relative impact of

the predictors on the IPGS, IOP category had the strongest influence ($\beta = 4.191 \pm 0.446$), followed by stage of POAG at presentation, disease duration and patient age. Second, an equation was developed for calculation of IPGS, with a significant effect of the combination of independent variables on the dependent variable ($R = +0.965$ ($F = 562.35$, $P < .0001$); adjusted $R^2 = +0.931$).

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Table 1. Values of IPGS at 2 years following different POAG stages at baseline and the results of discriminant analysis of the effect of these stages on the index

Stage:	1	2	3	4	F	p
	15.91±0.70	25.00±1.10	31.17±1.30	40.00±1.90	104.91	< 0.0001

Note: IPGS, index of progression of glaucoma stage; POAG, primary open-angle glaucoma

Table 2. Correlation of independent variables at baseline and IPGS

Independent Variable	IPGS	
	r	P
Sex	-0.169	0.027
Age	-0.498	<0.0001
Disease duration	0.695	<0.0001
POAG stage at baseline	0.805	<0.0001
IOP category	0.735	<0.0001

Note: IOP, intraocular pressure; IPGS, index of progression of glaucoma stage; POAG, primary open-angle glaucoma

Table 3. Results of regression analysis for the dependent variable (IPGS)

Variable	β	SE β	t	p
Free term	35.311	1.442	24.485	<0.0001
Age	-0.521	0.022	-23.246	
Disease duration	2.512	0.313	8.0104	
POAG stage at baseline	3.913	0.356	10.983	
IOP category	4.191	0.446	9.391	

Note: β , regression coefficient; IOP, intraocular pressure; IPGS, index of progression of glaucoma stage; POAG, primary open-angle glaucoma; SE β , standard error of regression coefficient; t, Student test value; p, statistical significance

Table 4. Results of the analyses of residuals, observed IPGS values and calculated IPGS values

Characteristics	Observed	Calculated	Residuals
M ± m	28.79±0.84	28.79±0.81*	-2.3E-10±0.22
IPGS min.	12.73	11.13	-6.85
IPGS max.	56.76	51.70	6.52
Med	27.76	29.09	-0.15
Mod	13.56	12.67	0.88

Notes: M, mean value; m, – mean error; min, max, minimum and maximum values, respectively; Med, median; Mod, mode; *, p = 0.49 (difference between observed and calculated means)

