



ORIGINAL ARTICLE

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Sensitivity and Specificity of Diagnostic Procedures in Primary Open-Angle Glaucoma

Bojana Markić,¹
Milka Mavija,¹
Vesna Ljubojević,¹
Emira Ignjatić

¹ Eye Disease Clinic, University Clinical Centre of RS, Banjaluka, University of Banja Luka/Faculty of Medicine, Banjaluka, Republic of Srpska, Bosnia and Herzegovina

ABSTRACT

Introduction. It can be difficult and challenging for an ophthalmologist to diagnose Primary Open Angle Glaucoma (POAG), particularly in its early stage, due to inherent variability in the general population as well as inability to make a clear distinction between normal condition and glaucoma. The degree of sensitivity and specificity of the diagnostic procedures applied in the diagnostics and monitoring of glaucoma may have a significant impact on the accuracy of diagnosis of POAG.

Aim of the study. To determine the degree of sensitivity and specificity of available tests for the diagnosis of POAG in the observed sample of subjects.

Patients and Methods. A prospective cross-section study was used to collect data referring to diagnostic procedures applied in 30 healthy subjects (30 eyes) of the control group and 30 newly diagnosed patients with POAG (30 eyes) of the target group, where the sensitivity, specificity and overall diagnostic precision of the diagnostic procedures in diagnosing glaucoma were evaluated.

Results. The stereoscopic assessment of vertical Cup/Disc ratio proved to be the diagnostic test with the highest precision, along with the highest grade of sensitivity and specificity for diagnostics of glaucoma, presented in the following values: 94.7%, 89.3% and 86.7 %, respectively.

Conclusion. Stereoscopic evaluation of vertical Cup / Disc ratio is a generally accepted, simple and inexpensive method for diagnosing glaucoma in daily clinical practice, while this parameter is of low diagnostic value, if viewed in isolation. It is necessary to combine as many available diagnostic procedures as possible in order to provide higher precision in diagnosis of glaucoma.

Key words: primary open-angle glaucoma, diagnostics, sensitivity, specificity

Contact address:

Bojana Markić
Eye Disease Clinic,
University Clinical Center of RS,
Banja Luka
12 beba bb, 78000 Banja Luka
bojana.markic@gmail.com

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Introduction

The diagnosis of Primary Open Angle Glaucoma (POAG), particularly in its early stage, can be difficult to make due to inherent extensive variability in the population as well as due to lack of clear distinction between the normal condition and glaucoma. Such variability is already present in the size of Optic Disc Papilla (papilla nervi optici /PNO/, or optical nerve head /ONH/), in the size of its cupping, the total number of axons per eye, in the variability of visual field threshold sensitivity, as well as sensitivity and tolerance to the increased intraocular pressure (IOP). Moreover, the degree of sensitivity and specificity of the diagnostic procedures applied in the diagnosis and monitoring of glaucoma is also of great significance.

Currently, the diagnostic procedure of POAG implies comprehensive general eye examination, gonioscopy, measurement of Central Cornea Thickness (Pachymetry), determining diurnal variation of IOP, ophthalmoscopy, perimetry, stereo photography imaging diagnostics, as well as use of imaging technologies such as Optical Coherence Tomography (OCT), Scanning Laser Polarimetry (SLP) and Confocal Scanning Laser Ophthalmoscopy (CSLO), which all aim to diagnosing POAG as early and as objectively as possible.

Heidelberg Retina Tomograph 3 (HRT 3) is a CSLO instrument that provides measurements of a number of stereometric parameters for ONH. This method entails two classification algorithms: Moorfields Regression Analysis (MRA) and Glaucoma Probability Score (GPS), based on which it assesses probability of the healthy or structurally changed papilla/ONH.¹ Apart from global analysis of papilla, HRT 3 provides measures per sectors, thus calculating stereometric quantitative parameters and classification algorithms for each of the six preliminarily redefined sectors.

Aim of the study

To determine the sensitivity and specificity of available POAG diagnostic tests in the observed sample of subjects.

Patients and Methods

Within the period from November, 2014 to April, 2015, a prospective cross-section study was carried out in the Eye Clinic of the RS University Clinical Center, which examined two groups of 30 patients (30 eyes) each, matched for age and regardless of the sex. All subjects were supposed to be aged 18 or older, conscious and well-oriented in all three dimensions, to have signed Informed medical consent form and to have the best corrected visual acuity (Snellen charts) of 0.5 or better. Gonioscopic findings should have indicated a wide open iridocorneal angle.

The target group comprised of subjects with newly diagnosed POAG, normal tension glaucoma (NTG), Ocular Hypertension (OH) or POAG suspected (Glaucoma suspecta). The diagnosis of POAG, NTG or OH was made based upon clinical examinations, as well as structural and functional modifications.

The control group comprised of healthy subjects with IOP in both eyes ≤ 21 mmHg, bilaterally normal visual field (VF) test findings, normal findings on ONH and Retinal Nerve Fiber Layer (RNFL).

All subjects underwent complete eye examination, gonioscopy, stereo-ophthalmoscopy in medicamentous mydriasis, stereoscopic photography of ONH with fundus camera, diagnostics with HRT 3 (stereometric analysis, MRA and GPS) and visual field test obtained by Octopus 900 pro perimetry (program G Standard / W-W / Normal).

Only high quality HRT scans were analyzed, with the result of more than 90% sensitivity and a standard deviation up to 30 μm .

The subjects underwent the test of modified daily curve of Intraocular Pressure when sitting (measurements of IOP were taken at 7:30 a.m., 1:30 p.m. and 7:30 p.m.) and it was considered as positive for IOP fluctuation ≥ 5 mmHg.

In visual field test analyses, the classification used was Hodapp -Anderson - Parish (H-A-P) scale² for positive ophthalmology opinion, as well as for preliminary, moderate or advanced glaucoma phase.

Stereo-photographic tests encompassed the analysis of the following indicators: assessment of vertical Cup/Disc (C/D) ratio, deviations from the „ISNT rule“ (in healthy optic nerves, the Inferior Neuroretinal rim thickness is the widest one, then followed by Superior, Nasal and Temporal; Inferior \geq Superior \geq Nasal \geq Temporal), neuroretinal rim cupping, the nasalization of funnel-shaped vessels in papillae, phenomenon of vessels bayoneting at the optic rim, acquired papilla demarcation, papillary disc hemorrhage, modifications in the lamina cribrosa, peripapillary atrophy (α and β zone), diffuse deficits of RNFL, localized deficits of RNFL and asymmetry of the papilla cupping.

HRT 3 exams were used for analysis of global stereometric parameters: papilla disc area, cup/ disc area ratio, linear cup/disc ratio, cup shape measure, neuroretinal rim area, neuroretinal rim volume, height variation contour and mean RNFL thickness.

The results obtained by Moorfields Regression Analysis (MRA) and Glaucoma Probability Score (GPS) were analyzed per redefined PNO segments as well as for papilla globally. Each of these parameters was classified to fall within either of the following: within normal limits (WNL), borderline (BL) or exceeding normal limits (ENL). MRA and GPS results obtained were analysed in line with two criteria. The first criteria implied the borderline result as Test-negative – the most specific criteria, that is, the borderline result was observed as healthy. The other criteria implied to borderline cases as Test-positive – the least specific criteria, that is, the borderline results were observed as pathological.

In both groups of subjects, results obtained upon examination of a single eye were analyzed. In the target group, the “worst” eye was analyzed (i.e. the eye with the worst PNO examination results, and/or worst vision field test results, and/or higher IOP), however in the control group, the results obtained with examination for the right eye (OD) were analyzed.

Criteria for exclusion from the case study were as follows: positive personal ophthalmologic history or prior eye trauma diagnosed upon clinical examination, inflammatory process in terms of uveitis, or intraocular laser or surgery intervention, significant blur in optical medium, retinal disease or non-glaucomatous optic neuropathy.

In order to be able to assess the set goal, upon all diagnostic tests (the test of modified daily IOP- curve, stereophotography of PNO and RNFL, visual field test, stereometric parameters analysis, MRA and GPS obtained with HRT), parameters that proved to be the most statistically significant in terms of the highest sensitivity, specificity and overall diagnostic precision in diagnosing glaucoma were selected.

The statistical processing of all parameters implied use of the IBM SPSS Statistics 20.0 package, the descriptive statistics in describing the sample, and Receiver Operating Characteristic (ROC) curve for demonstration and evaluation of the sensitivity/specificity of the diagnostic tests. Results are presented in Tables and Graphs, and the result of $p < 0.05$ was deemed the statistically significant difference.

Results

The research encompassed the sample of 60 subjects (60 eyes) divided into the control group and target group, each comprising of 30 subjects (30 eyes). 48.28% of the total number of subjects had glaucoma. Two subjects diagnosed with Glaucoma Suspecta were not included in analyses of sensitivity and specificity, the results of which follow. Demographic characteristics of subjects are shown in Table 1.

Table 1. Demographic characteristics

Parameters		Target groups			p
		Control (n=30)	Target (n=30)	Total (n=60)	
Sex n (%)	Male	10 (33.33)	9 (30)	19 (31.67)	0.781*
	Female	20 (66.67)	21 (70)	41 (68.33)	
Age group (AG)		Male	62.23 (8.95)	62.43 (7.74)	0.843**
Target group /Diagnosis					
		POAG (n)	21		
		NTG (n)	3	48,28% (od n=60)	
		OH (n)	4		
		Glaucoma suspecta (n)	2		

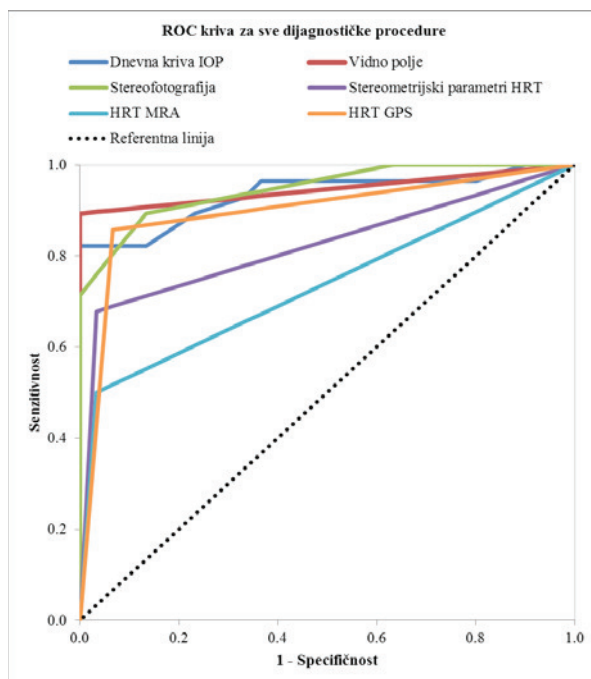
SD=standard deviation; * = χ^2 test; ** = Student test ; POAG- Primary open-angle glaucoma; NTG- Glaucoma normotensivum; OH-Ocular hypertension

IOP=intraocular pressure; HRT=Heidelberg Retina Tomograph; MRA=Moorfields Regression Analysis; GPS=Glaucoma Probability Score; T=temporal; TI=temporo-inferior; N=nasal; NS=nasal-superior; NI=nasal-inferior

Table 2. Predictive indicators of individual diagnostic tests

Diagnostic tests	Sensit.	Specif.	95 % CI		AUC	p
			Lower border	Upper border		
IOP at 7.30 a.m.	0.821	0.867	0.864	1.000	0.934	< 0.001
Vertical Cup/Disc (stereophotography)	0.893	0.867	0.893	1.000	0.947	< 0.001
Visual Field Test	0.892	1.000	0.878	1.000	0.946	< 0.001
Cup/Disc Area Ratio(HRT 3.0)	0.678	0.966	0.707	0.938	0.823	< 0.001
MRA TI (the most specific criteria)	0.500	0.967	0.441	0.738	0.589	0.015
GPS global, T, TI, N, NS and NI (the least specific criteria)	0.857	0.933	0.803	0.988	0.895	< 0.001

IOP=intraocular pressure; HRT=Heidelberg Retina Tomograph; MRA=Moorfields Regression Analysis; GPS=Glaucoma Probability Score; T=temporal; TI=temporo-inferior; N=nasal; NS=nasal-superior; NI=nasal-inferior

Graph 1. Receiver Operating Characteristic (ROC) analysis of predictive indicators for individual diagnostic tests

Diagnostic test with the highest sensitivity of 89.3% was the indication forevaluation of vertical Cup/Disc ratio from the stereography of papillae, but this diagnostic test also proved to have the highest overall precision in diagnosing glaucoma, with the computed value of 94.7%. The Field Vision Test based upon H-A-P classification proved to have the highest specificity of 100%.

Discussion

Increased IOP and its fluctuations are one of the most important risk factors for Glaucoma incidence and progression.³ An alternative to the unpractical 24-hours IOP monitoring is the modified diurnal IOP curve that implies three to five IOP measurements starting from 7.00 a.m. until 8.00 p.m. with equal intervals between the measurements. However, this test could fail to demonstrate up to 70% of IOP peaks due to IOP variability, as well as because more than 70% of IOP peaks occur around 6.00 a.m. while the subject is in supine position (in the lying on the back position).⁴

Our results indicated that the values of average IOP in both groups were the highest when measured at 7.30 a.m. with sensitivity and specificity of 82.1% and 86.7%, respectively (0.864; 1.000), which is similar to the results of other studies.⁵ Bonomi and associates⁶ examined the diagnostic validity of tonometry in population-based cross-sectional study and they found sensitivity and specificity for tonometry to be 80.1% and 97.8%, respectively (with the cut-off IOP value from 21 to 22 mmHg).

In our study, stereography analysis depicted a parameter of vertical cup/disc ratio with the highest overall precision of 94.7% as well as the highest sensitivity of 89.3% along with specificity of 86.7%.

In 15 healthy subjects and 15 subjects with POAG, Zangwill and associates⁷ examined compliance in evaluation of vertical C/D ratio between CSLO and PNO stereoscopic photography, which was evaluated separately by three experienced clinicians, respectively. They found sensitivity and specificity for assessment of vertical C/D ratio based upon stereography to be different for each examiner, and

examiner A obtained the values of 47% and 93%, examiner B obtained the values of 47% and 100%, and examiner C obtained the values of 60% and 93%, respectively. Both clinical study and population-based study indicated low sensitivity from 52% to 64% and specificity from 57% to 89% for vertical C/D ratio, in order to distinguish healthy papillae against papillae with early glaucoma.

The assessment of vertical C/D ratio is the approach most commonly used by clinicians for evaluation of glaucomatous damage of papilla. When observed isolated, this parameter has limited value for identifying glaucoma due to examiners' subjectivity and extensive variation among healthy population in terms of papilla size and cup/disc ratio.

From the above mentioned, we may also conclude for our study that subjectivity of the examiner, the number of participants and the stage of glaucomatous damage had significant impact on the sensitivity and specificity values for the parameter of vertical C/D ratio.

The values for sensitivity and specificity of 89.2% and 100.0% that we obtained with vision field test are similar to values obtained by other examiners, whose values for sensitivity and specificity varied within the range from 83% to 93%, depending upon the criteria applied in diagnosing glaucomatous defects.⁸

Ophthalmology papers confirming the high sensitivity and specificity of vision field test against the diagnosis of glaucoma are publicized almost regularly. However, it should not be neglected that vision field test may diagnose glaucomatous vision loss only upon irreversible loss of more than 40% of retinal neural tissue. Vision field test is also greatly affected by subjectivity of examinee, short-term or long-term fluctuation as well as by yet unachieved consensus in terms of classification of assessment of vision field damage.

Results of our study obtained by HRT 3 indicated stereometric parameter of cup/disc area ratio with the highest sensitivity and specificity values of 67.9% and 96.7%, respectively, as well as with the highest overall precision of 82.3% (0.707; 0.938). Our results were similar to results obtained in other studies^{5,9,10} which established the highest precision for the parameter of cup/disc area ratio ranged from 84.2% to 86.5%, along with sensitivity of 74.2% for fixed specificity of 85%.

The MRA in our sample indicated the Temporal-Inferior sector to have the highest sensitivity and specificity of 50.0% and 96.7%, respectively (0.441; 0.738), with the highest overall precision for detecting glaucoma of 73.3% (0.599; 0.867), for borderline results viewed as positives.

Up to now, different values of sensitivity and specificity of MRA were reported, due to extensive variability in the shape and size of papillae in healthy subjects against those having POAG pathology, the effect of glaucoma stage, the race, as well as the effect of examiner's subjectivity on the obtained results.

GPS algorithm eliminates the factor of examiner's influence that is considered important reason for variability. Coops and authors¹¹ determined for GPS the sensitivity and specificity of 59% and 91% respectively for borderline results viewed as test-negative, and 78% and 63% respectively, for borderline results that were viewed as test-positive, along with the overall diagnostic precision of 78%. They found that GPS classification within certain sectors seemed to correlate a lot, adding little or no information to the one already available in the global classification.

GPS in our study indicated that global classification and all sectors other than Temporal-Superior (TS) show the highest and uniform sensitivity and specificity of 85.7% and 93.3% respectively and entailed the highest overall accuracy of 89.5% (0.803; 0.988) in borderline results as test-positive.

Moreno-Montañés and associates,¹² taking borderline results as positive, obtained the sensitivity of 83.1% for Nasal and Nasal-Superior sector with the specificity value of 59.3%. According to this criterion, GPS global obtained the highest sensitivity value of 85.5%, while with somewhat lower value for specificity of 54.2%. With this criterion, the Temporal-Inferior sector computed the sensitivity and specificity values of 80.7% and 59.3%.

Oddone and associates¹³ examined diagnostic capacity of the sectoral HRT 3 analysis in terms of differentiating between healthy and glaucomatous eyes, and according to their study, Temporal-Inferior sector had the largest area under the ROC curve of 74%. Also, both GPS and MRA tests demonstrated the highest diagnostic precision in the Temporal-Inferior sector with the sensitivity and specificity of 63% and 88% for MRA test and, 80% and 62% for GPS test, respectively.

Reviewing our results for these two HRT 3 tests, the MRA as examiner-dependent algorithm and the GPS as the one that is examiner-independent, we may derive the following conclusion: that in both tests, the results of the target group showed statistically significant difference from the ones of the control group; that percentage values for sensitivity and specificity in both MRA and GPS turned out to be higher when computed in line with the least specific criteria; that diagnostics capacity of both MRA and GPS in detecting healthy subjects was excellent and estimated to 96.7% for MRA and 93.3% for GPS; that Temporal-Inferior

sector was distinguished as a particularly significant sector with the highest value of sensitivity, specificity and overall diagnostic precision in diagnosing glaucoma, which is in compliance with applicable clinical knowledge and results produced by other studies, which determined that an initial glaucoma is easiest detected in the Temporal-Inferior sector of PNO; that it is necessary to pay special attention to the sectoral characteristics of papillae, since these information could provide us with more precise discrimination between healthy and glaucomatous papillae.

Conclusion

In our study, stereoscopic valuation of vertical cup/disc ratio proved to be the diagnostic test with the highest overall precision in diagnosing glaucoma, with a value of 94.7%. Additionally, it is the test that provides the highest sensitivity of 89.3%, along with specificity of 86.7%.

Each of the diagnostic procedures that we conducted was observed in numerous studies as a part of the screening program for the diagnosis of glaucoma. Which test was ranked as more or less significant would vary from study to study. However, what was well noticeable is that no study proposed elimination of any diagnostic test, while rather recommending the need to combine as many diagnostic procedures as available, with the aim to make as early and precise diagnosis of Primary Open Angle Glaucoma (POAG) as possible.

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Senzitivnost i specifičnost dijagnostičkih procedura kod primarnog glaukoma otvorenog ugla

SAŽETAK

Uvod. Zbog postojanja varijabilnosti u opštoj populaciji i nemogućnosti jasnog razgraničenja između normalnosti i glaukoma, dijagnoza primarnog glaukoma otvorenog ugla (Primary open-angle glaucoma, POAG), naročito u ranom stadijumu, može biti problematična i predstavlja izazov za oftalmologa. Značajan uticaj na tačnost postavljanja dijagnoze POAG imaju i stepen senzitivnosti i specifičnosti dijagnostičkih procedura koje se primjenjuju u dijagnostici i praćenju glaukoma.

Cilj rada. Utvrditi senzitivnost i specifičnost nama dostupnih testova za dijagnostiku POAG na posmatranom uzorku ispitanika.

Ispitanici i metode. Prospektivnom presjek studijom prikupljeni su podaci dijagnostičkih procedura sprovedenih kod 30 zdravih ispitanika (30 očiju) kontrolne grupe i 30 novootkrivenih pacijenata oboljelih od POAG (30 očiju) ciljne grupe i vršena je procjena njihove senzitivnosti, specifičnosti i ukupne dijagnostičke preciznosti za dijagnostikovanje glaukoma.

Rezultati. Dijagnostički test sa najvećom ukupnom preciznošću za dijagnostikovanje glaukoma, najvećom senzitivnošću i najvećom specifičnošću je stereoskopska procjena vertikalnog Cup/Disc odnosa sa vrijednostima od 94,7%, 89,3 % i 86,7 %, redom.

Zaključak. Stereoskopska procjena vertikalnog Cup/Disc odnosa je opšte prihvaćena, jednostavna i jeftina metoda za dijagnostikovanje glaukoma u svakodnevnoj kliničkoj praksi, ali je od niske dijagnostičke vrijednosti ukoliko se ovaj parametar posmatra izolovano. S ciljem što preciznijeg postavljanja dijagnoze glaukoma, potrebno je kombinovati što više dostupnih dijagnostičkih procedura.

Ključne riječi: primarni glaukom otvorenog ugla, dijagnostika, senzitivnost, specifičnost