Comparison of glaucoma probability score and Moorfields regression analysis to discriminate glaucomatous and healthy eyes

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PURPOSE. *To compare sensitivity and specificity values of glaucoma probability score (GPS) and Moorfields regression analysis (MRA) of Heidelberg retina tomograph (HRT) to discriminate between glaucomatous and healthy eyes.*

METHODS. *A total of 160 eyes of 160 individuals (80 glaucoma patients and 80 healthy subjects) were enrolled in this prospective cross-sectional study. Confocal scanning laser ophthalmoscopy was performed with HRT. Performance of GPS and MRA were evaluated by considering borderline (BL) cases as within normal limits (WNL) or as outside normal limits (ONL). For further analysis glaucoma group was divided into two subsets: initial and moderate/severe damage group.*

RESULTS. *There was no difference between glaucoma patients and normal subjects in terms of gender, disc area, and pachymetry (p>0.05). The GPS was higher, average visual field MD and PSD values were worse, and patients were older in glaucoma group (p=0.001). Sensitivity and specificity values were 72.5% and 93.8% respectively for MRA and 75.0% and 88.8% for GPS when BL cases considered as WNL, and when BL cases considered as ONL these values were 83.8% and 73.8% for MRA and 88.8% and 70.0% for GPS. There was no difference between sensitivity and specificity values of GPS and MRA for either situation (p>0.05). Sensitivity of GPS (76.2%) was higher than of MRA (61.9%) in initial glaucomatous eyes (p=0.317).*

CONCLUSIONS. *Diagnostic performance of GPS was similar to MRA. It was found that GPS might differentiate between glaucomatous and healthy eyes with relatively better sensitivity but worse specificity and represent considerable advantage over MRA in early glaucoma cases. (Eur J Ophthalmol 2009; 19: 207-13)*

KEY WORDS. *Glaucoma, Heidelberg retina tomograph, Glaucoma probability score, Moorfields regression analysis*

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INTRODUCTION

Primary open angle glaucoma is a progressive multifactorial optic neuropathy leading to loss of vision characterized by loss of ganglion cells and axons, and is one of the major causes of blindness in the world (1, 2). It is therefore important to provide an estimate of early diagnosis of the disease and distinguish early signs of glaucomatous optic disc damage from normal optic nerve appearance.

The Heidelberg retina tomograph (HRT: Heidelberg Engineering GmbH, Heidelberg, Germany), a confocal scanning laser ophthalmoscopy device, has been shown to be capable of detecting the structural alterations in glaucoma and widely used as a tool for optic disc analysis. It acquires three-dimensional topography images of the optic disc and the surrounding retina objectively. The HRT pro-

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vides rapid and highly reproducible measurements of the optic nerve head (3-5) and the calculated quantitative morphologic parameters may discriminate between healthy and glaucomatous eyes (5-7).

The Moorfields regression analysis (MRA) was developed to improve the diagnostic accuracy of the HRT, which uses estimates from global and six sectors of neuroretinal rim area adjusted for optic disc size and age (7-9). Until recently, many of the quantitative measurements and diagnostic analysis of the HRT depended on the manually placed contour line to outline the area of the optic disc at the inner border of scleral ring, which introduced some subjectivity to the analysis of topographic measurements as contour lines drawn by different observers varied. To solve this problem, a new system has been incorporated into the software of the HRT (HRT 3) which does not rely on the manually drawn contour line and which includes an expanded normative database. This automated, operator independent classifying procedure of the optic disc analysis, glaucoma probability score (GPS), is based on a technique proposed by Swindale et al (10). The GPS calculation is based on the overall shape of the optic nerve head and posterior pole and does not rely on the outlining of the disc margin. The technique provides stereometric data by applying an automatic model of the optic nerve head shape (10). Recent studies have shown similar to improved discriminatory ability of the HRT 3 compared with HRT II (11-15). Both the MRA and GPS provide color-coded classifications simplifying the interpretation.

In this study, we aimed to evaluate the clinical usefulness of HRT examinations by assessing the sensitivity and specificity of the GPS and MRA classifications, for discriminating between healthy and glaucomatous eyes. We also aimed to determine the usefulness in subgroups, in terms of different visual field mean deviation values in glaucomatous eyes.

METHODS

In this prospective cross-sectional study, 160 eyes of 160 subjects (80 patients with primary open angle glaucoma and 80 healthy control subjects) were evaluated. Only the right eye was chosen for each subject.

All patients enrolled in this study agreed to participate and met the inclusion criteria and signed an informed consent agreement before any procedures were performed. The study was approved by the hospital's ethics committee and was performed in accordance with the ethical principles as described in the Declaration of Helsinki.

All of the patients included in this study underwent a complete ophthalmologic evaluation: Snellen visual acuity measurements, biomicroscopy of the anterior segment, gonioscopy, and posterior segment examinations were performed and IOP measurements were done by means of Goldmann applanation tonometry. Automated standard static threshold perimetry was performed with the Humphrey Field Analyzer (Zeiss Humphrey Instruments, San Leandro, CA) using the Swedish interactive threshold algorithm (SITA) 30-2 strategy. Each patient's CCT was measured three times with an ultrasonic pachymeter (BVI pachymeter, B.V. International, Clerment-Ferrand, France) and the mean of these measurements was taken for statistical analysis. Confocal scanning laser ophthalmoscopy with the HRT (Heidelberg Engineering, GmbH, Heidelberg, Germany) was performed in a standardized manner. A contour line was carefully drawn for analysis of the image by a single, experienced observer, T.T., and all analysis on the HRT was performed using HRT software version 3.0.

The inclusion criteria were best-corrected visual acuity of ≥20/25 and a refractive error not exceeding 5.00 diopters sphere and/or 2.00 diopters cylinder; exclusion criteria were optic disc abnormality, all eye diseases other than POAG, a history of neuroophthalmologic diseases, HRT images with poor quality, intraocular surgery or laser surgery, and severe ocular trauma at any time.

The normal control subjects had an IOP of ≤21 , normal optic disc appearance (no diffuse or focal neuroretinal rim thinning, no disc hemorrhage, and no RNFL defects on red-free examination) and a normal visual field (normal glaucoma hemifield test results and a mean deviation and pattern standard deviation [PSD] values within 95% confidence limits).

The glaucoma patients had an IOP of >21 , and repeatably detectable glaucomatous visual field defects with optic nerve damage. The defect was defined as a glaucoma hemifield test result outside normal limits and/or PSD outside of the 95% normal limits.

Details of the confocal scanning laser ophthalmoscopy have been described previously (16). The principles of the analysis underlying the GPS have been described by Swindale et al (10). The GPS analysis outputs ranges from 0% to 100%. Scores from 0% to 27% are categorized by the software as within normal limits (WNL), 28% to 64% as borderline (BL), and 65% to 100% as outside normal

limits (ONL) (15). The overall outcome of the GPS analysis is determined by the sector with the highest probability score (worst result of global and sectoral analysis).

The MRA has been described by Wollstein et al (17). If the observed rim area from the subject's eye is 95% or more of the prediction interval based on distribution found in a group of normal subjects, it is categorized as WNL. The results from the MRA are BL if the rim area is between the 95% and 99.9% prediction interval, and ONL if the rim area is less than the 99.9% prediction limit. The overall outcome of the MRA is determined by the most abnormal sector, similar to the GPS analysis.

Both GPS and MRA have borderline category for the optic discs which cannot be identified as normal or outside normal limits. That is why we evaluated the performance of GPS and MRA in two different ways, first by considering borderline cases as normal (most specific, least sensitive) and second by considering borderline cases as outside normal limits (most sensitive, least specific).

For further analysis the glaucoma group was divided into two subsets according to the subject's level of visual field loss. The classification was made according to the Hodapp-Parrish-Anderson score (18) by checking values of each single point besides the MD values. In the initial damage group mean deviation was >–6 dB, and in the moderate and severe damage group the mean deviation was below ≤–6 dB.

Statistical analysis was performed using SPSS 13.0 for Windows (SPSS Inc.). Independent-samples *t* test was used to compare glaucomatous and normal eyes. Group comparisons were conducted for categorical variables using chi-square tests. Sensitivity and specificity values were calculated for the MRA and GPS classifications. Evaluation of agreement between the two techniques was performed with Kappa statistics for each group and the Kappa coefficient was calculated. The significance level was set at 5% and a two-way analysis was used for all tests.

RESULTS

Eighty eyes of 80 patients with primary open angle glaucoma and 80 eyes of 80 healthy subjects were enrolled in this study. The demographic and ocular characteristics of the study population are summarized in Table I. Glaucoma patients were significantly older than the healthy subjects (p=0.001). The average visual field MD and PSD values were worse in the glaucoma group (p=0.001) due to the selection of patients. The calculated GPS was 69.9±23.2% in glaucoma patients, which was again higher than the normal control subjects (p=0.001). There was not difference in terms of gender, disc area, and pachymetry between the groups (p>0.05).

The number of overall HRT classifications as WNL, BL, and ONL with GPS and MRA methods in glaucomatous and healthy normal eyes are shown in Table II. There was a statistically significant difference between the groups for both GPS and MRA classifications (p=0.001). The glaucoma group was further divided into two subsets classified as initial glaucoma and moderate/severe glaucoma according to the subject's level of visual field loss and the GPS and MRA classifications for these two groups are also shown in Table II.

There was no difference between sensitivity and specificity values of GPS and MRA to discriminate between glaucomatous and normal eyes when BL cases were considered either ONL or WNL (p>0.05) (Figs. 1 and 2). Although the sensitivity of GPS (76.2%) was higher than the sensitivity of MRA (61.9%) in initial damage group of glauco-

TABLE I - DEMOGRAPHIC AND OCULAR CHARACTERISTICS OF THE STUDY POPULATION

	POAG (n=80)	Normal (n=80)	p value
Age (years)	63.5±9.9	53.6±11.1	0.001
Sex (male/female)	49/31	45/35	0.521
Disc area (mm^2)	2.1±0.3	2.0±0.3	0.125
Pachymetry (µm)	542.3±48.3	553.8±50.3	0.142
GPS (%)	69.9±23.2	27.4±19.5	0.001
MD (dB)	–6.9±4.8	–0.6±2.1	0.001
PSD (dB)	5.7±3.6	1.2±0.6	0.001

POAG = primary open angle glaucoma; GPS = glaucoma probability score; MD = mean deviation; PSD = pattern standard deviation.

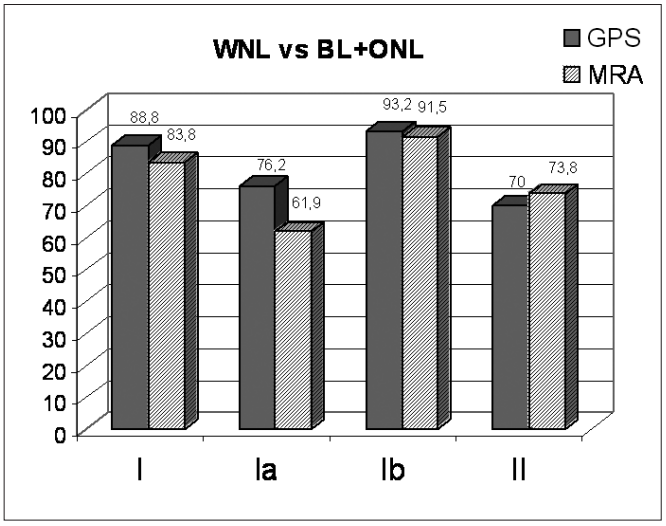

Fig. 1 - *Sensitivity and specificity of glaucoma probability score (GPS) and Moorfields regression analysis (MRA) to discriminate between glaucomatous and normal eyes when borderline (BL) cases were considered as outside normal limits (ONL) (within normal limits [WNL] vs BL + ONL). I = sensitivity total; Ia = sensitivity initial glaucoma; Ib = sensitivity moderate/severe glaucoma; II = specificity.*

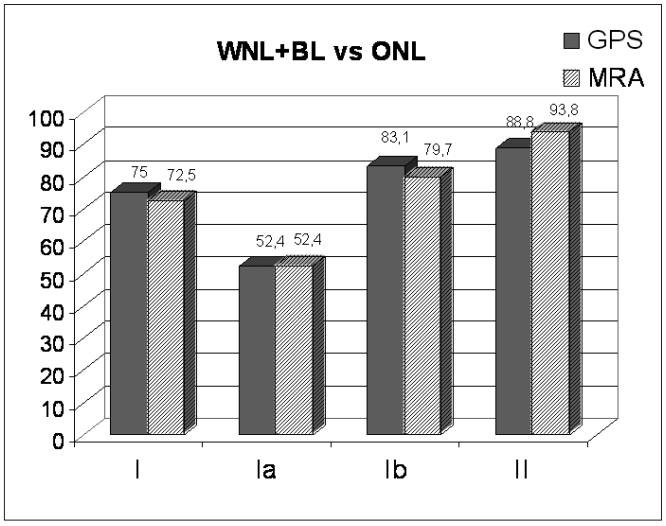

Fig. 2 - *Sensitivity and specificity of glaucoma probability score (GPS) and Moorfields regression analysis (MRA) to discriminate between glaucomatous and normal eyes when borderline (BL) cases were considered as within normal limits (WNL) (WNL + BL vs outside normal limits [ONL]). I = sensitivity total; Ia = sensitivity initial glaucoma; Ib = sensitivity moderate/severe glaucoma; II = specificity.*

TABLE II - OVERALL HRT CLASSIFICATIONS WITH GPS AND MRA IN GLAUCOMATOUS AND HEALTHY EYES

	POAG (n=80)		Normal (n=80)	p value*
	Total	Initial/moderate and severe		
GPS				
WNL	9 (11.2%)	5/4	56 (70.0%)	
BL	11 (13.8%)	5/6	15 (18.8%)	0.001
ONL	60 (75.0%)	11/49	9 (11.2%)	
MRA				
WNL	13 (16.3%)	8/5	59 (73.8%)	0.001
BL	9 (11.2%)	2/7	16 (20.0%)	
ONL	58 (72.5%)	11/47	5 (6.2%)	

*Comparison of healthy and glaucomatous (total) eyes.
HRT = Heidelberg retina tomograph; GPS = glaucoma probability score; MRA = Moorfields regression analysis; POAG = primary open angle glaucoma; WNL = within normal limits; BL = borderline; ONL = outside normal limits.

matous eyes, it was not statistically significant (p=0.317) (Fig. 1). It was found that sensitivity was relatively higher than specificity when the analysis of the GPS and MRA were performed considering the BL classification as ONL (Fig. 1), and specificity was relatively higher than sensitivity when BL classification was considered as WNL (Fig. 2). It was also seen that the sensitivity values of both GPS and MRA were higher in the moderate/severe visual field damage group than initial damage group when BL cases were considered either WNL or ONL (p<0.05).

Kappa value was 0.822 (p<0.001) in glaucoma patients and 0.801 (p<0.001) in normal subjects, showing that the two techniques had almost perfect agreement.

DISCUSSION

Detecting glaucomatous changes of the optic nerve head by HRT has been widely validated (3, 4, 6, 7, 17, 19, 20). The HRT is easy to perform, provides quantitative data, and offers an initial approach to discriminate between glaucomatous and normal eyes based on a normative database. The outcomes of MRA and GPS classifications are very easy to read and had similar diagnostic performances. But clinicians should be aware of the strength and limitation of HRT classifications while making decisions in clinical practice. In this study we compared the GPS classification with the MRA classification.

MRA is used for classifying optic nerve head as WNL, BL or ONL. One of the limitations of MRA is that it depends on the position of the contour line. Besides, further evaluation is needed to determine the efficacy of the machine in the early detection of glaucomatous optic nerve head damage. Therefore GPS classification, which is a contour line independent and a fully automated method, is an important advance in HRT machine. The GPS is a probability value of disease and it represents the likelihood of glaucoma. It does not show the level of damage. In this study, the GPS was 69.9% in glaucomatous eyes and 27.4% in healthy eyes. It was found significantly higher in glaucoma patients.

Sensitivity and specificity depend on the specific cutoff points used to define the disease. The BL category is defined for the optic discs which cannot be identified as WNL or ONL. In our study, more BL cases were seen in healthy eyes than glaucomatous eyes, for both GPS and MRA classifications. It is important to determine in which group the BL category is included for both GPS and MRA. That is why in this study we calculated the sensitivity and specificity values considering the BL cases either WNL or ONL and we have seen that considering BL as WNL was most specific and least sensitive, and considering BL cases as ONL was most sensitive and least specific. There was no difference between sensitivity and specificity values of GPS and MRA in both situations.

Disc size and severity of visual field damage influence the diagnostic accuracy of both the GPS and MRA (21). Sensitivity improves with increasing disc size and severity of visual field damage. In large optic discs, both GPS and MRA were likely to produce many false positive classifications (13). In our study, mean disc sizes were similar in glaucomatous and healthy eyes, so we think that comparing the calculated values for these groups should not be affected by disc sizes.

The severity of the visual field loss has been shown to be important on imaging instrument sensitivity (22). Ferreras et al (14) showed that the GPS tended to have higher sensitivity and lower specificity than the MRA, especially when visual field tests indicated mild damage. They also concluded that the MRA had slightly better diagnostic ability than GPS for all degrees of visual field loss. The results of Miglior et al's (8) study showed that MRA was highly sensitive and specific when only normal and POAG patients were included in the study. However, the sensitivity was moderate and fairly constant when MD was within –12 dB, and it was extremely high only when MD was larger. Harizman et al (11) found that GPS sensitivity (72.3%) tends to be higher than that of the MRA sensitivity (59.6%) for detection of early glaucoma. Medved and Cvenkel (9) divided glaucoma patients into three groups as early, moderate, and advanced according to visual field loss and found sensitivity of MRA as 59.1%, 54.5%, and 92.8% when BL cases were considered WNL and 81.8%, 72.7%, and 100% when BL cases were considered ONL, respectively. In our study we have also seen that the sensitivity of GPS was higher than the sensitivity of MRA in initial damage group of glaucomatous eyes when BL cases were considered as ONL. The sensitivity values were nearly the same for GPS and MRA in moderate and severe damage group and the sensitivities were higher than the initial damage group. That is why GPS may be more useful than MRA in early glaucomatous eyes.

Coops et al (13) found that the MRA apparently depended on the age. With each decade of increasing age, the odds of BL and ONL result with the MRA increase in glaucoma patients and healthy subjects. It should be noted that age difference between groups might affect the results of this study. As mean disc sizes and some other parameters were similar between the groups, comparison of the calculated values might not be affected by age.

In some clinical studies, sensitivity was observed between 59 and 85% (8, 9, 12-14, 17, 22) and specificity was observed between 66 and 97% (8, 9, 12-14, 17, 22) for the MRA overall classification at 95% CI (considering BL as ONL). When BL values were considered WNL the sensitivity was found between 56 and 71% (11, 13, 21) and specificity was found to be 87–100% (11, 13, 21). In this study, the MRA discriminating performance for sensitivity and specificity was 72.5% and 93.8% for considering BL as WNL and 83.8% and 73.8% for considering BL as ONL, respectively.

Sensitivity was observed between 58 and 78% (12-14) and specificity was observed between 63 and 94% (12-14) for the GPS overall classification at 95% CI (considering BL as ONL). When BL values were considered WNL the sensitivity was found between 59 and 77% (11, 13, 21) and the specificity was found to be 82–91% (11, 13, 21). In this study, with the GPS, sensitivity and specificity were 75.0% and 88.8% (when BL was considered as WNL) and 88.8% and 70.0% (when BL was considered as ONL), respectively.

Our results suggest that both GPS and MRA have good sensitivity when BL cases were considered as ONL and good specificity when BL cases were considered as WNL. The diagnostic performance of GPS classification was similar to MRA classification. GPS analyses the optic disc in a contour line independent automated manner which eliminates a major source of variability in HRT measurements. Leon-Ortega et al (12) showed that the GPS automated classification showed similar sensitivity but a considerably lower specificity than MRA. Zangwill et al (21) and Ferreras et al (23) found that GPS results tended to have higher sensitivity but lower specificity than MRA results, as in our study.

In clinical practice, both GPS and MRA should be used for discriminating between healthy and glaucomatous eyes. In this study, the diagnostic performance of the contour line independent GPS analysis was similar to that of the MRA. It was found that GPS may differentiate between glaucomatous and healthy eyes with relatively better sensitivity but worse specificity, although the Kappa statistics showed almost perfect agreement between the two techniques. Even more, GPS represents considerable advantage over MRA in early glaucoma cases.

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