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Diagnostic accuracy of Heidelberg Retina Tomograph III classifications in a Turkish primary open-angle glaucoma population

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ABSTRACT.
Purpose: **This study aimed to evaluate the diagnostic accuracy of Moorfields regression analysis (MRA) and the glaucoma probability score (GPS) in primary open-angle glaucoma (POAG) and to measure the level of agreement between the two algorithms in classifying eyes as normal or abnormal in a Turkish population.**
Methods: **We prospectively selected 184 healthy subjects and 158 subjects with POAG, who underwent an ophthalmological examination, visual field analysis and imaging with the Heidelberg Retina Tomograph II, using HRT III software, Version 3.0. The diagnostic accuracies of the two classifications were measured when the borderline was taken as either normal (highest specificity criteria) or abnormal (highest sensitivity criteria). The agreement between them was calculated using the unweighted kappa (κ) coefficient.**
Results: **Optic nerve head topographic parameters showed statistically significant differences between the control and POAG groups ($p < 0.001$). The parameters with the highest area under the receiver operating characteristic curves were global GPS (0.86), cup : disc area (0.85), rim : disc area (0.85) and vertical cup : disc (0.85). According to the highest specificity criteria, MRA had a sensitivity of 67.7% and a specificity of 95.1%, whereas the GPS had a sensitivity of 70.9% and a specificity of 88.0%. According to the highest sensitivity criteria, MRA had a sensitivity of 81.0% and a specificity of 75.0%, whereas the GPS had a sensitivity of 89.2% and a specificity of 57.6%. A moderate agreement of 68% (233 eyes) with a κ coefficient of 0.51 was found between MRA and the GPS.**
Conclusions: **The GPS automated classification showed similar sensitivity to MRA, but considerably lower specificity, when applied in a Turkish population.**

Key words: glaucoma – glaucoma probability score – Heidelberg Retina Tomograph (HRT) III – Moorfields regression analysis – Turkish population

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Introduction

The Heidelberg Retina Tomograph (HRT; Heidelberg Engineering GmbH, Heidelberg, Germany) is a confocal scanning laser ophthalmoscope that acquires three-dimensional topographic images of the optic nerve head (ONH) and the parapapillary retinal nerve fibre layer (RNFL) with a high degree of discrimination between healthy and glaucomatous eyes (Miglior et al. 2001; Zangwill et al. 2001; De León-Ortega et al. 2006). One algorithm of the HRT is Moorfields regression analysis (MRA), which compares a subject's rim area with the predicted rim area for a given disc area and age, based on confidence limits of a regression analysis derived from a new database in which population ethnicity can be selected (Wollstein et al. 1998; Miglior et al. 2003). Disadvantages of MRA include the fact that its normative database contains only subjects of European ancestry with a limited range of disc area, and that it requires a trained operator to identify and delineate the border of the optic disc, which introduces some subjectivity to the analysis. The newer HRT III software includes an expanded normative database including subjects of European, African and Indian ancestry and calculates the glaucoma probability score (GPS), which uses two measures of parapapillary RNFL shape (horizontal and vertical RNFL curvature) and three measures of ONH shape (cup size, cup depth and rim steepness) for input into a vector machine-learning classifier that estimates the probability of the presence of damage consistent with glaucoma (Swindale et al. 2000; Coops et al. 2006; Harizman et al. 2006). This algorithm does not rely on a manually drawn contour line or reference planes.

The aim of this study was to evaluate the diagnostic accuracy of global MRA and GPS classifications in primary open-angle glaucoma (POAG) and to measure the level of agreement between the two algorithms in classifying eyes as normal or abnormal in a Turkish population.

Materials and Methods

The prospective study protocol was approved by the ethics committee of Hacettepe University School of Medicine. The study design followed the tenets of the Declaration of Helsinki. The study included one randomly selected eye in each of 184 healthy subjects and 158 subjects with POAG. All participants underwent a complete ophthalmic examination, including visual acuity (VA) measurement, anterior and posterior segment slit-lamp examination, gonioscopy, Goldmann applanation tonometry, standard achromatic perimetry (SAP) examinations (Swedish Interactive Threshold Algorithm [SITA]-standard automated perimetry, program 30-2, Humphrey Field Analyser II; Carl Zeiss Meditec, Inc., Dublin, CA, USA) and ONH imaging with HRT. The inclusion criteria required participating eyes to have best corrected VA $\geq 20/40$, refractive error of < 5 spherical dioptres and 2 D of cylinder and transparent ocular media. Eyes with parapapillary atrophy, tilted discs and indistinct disc borders were excluded from the study. All participants were required to have reliable visual field (VF) examinations with $< 25\%$ of false-positive errors, false-negative errors and fixation losses.

Patients were classified as having POAG if they had ONH or RNFL structural abnormalities (diffuse thinning, focal narrowing or notching of the optic disc rim, especially at the inferior or superior poles; documented progression of cupping of the optic disc; diffuse or localized abnormalities of the peripapillary RNFL, especially in the inferior or superior poles; disc rim or peripapillary RNFL haemorrhages; neural rim asymmetry between the two eyes consistent with loss of neural tissue) and/or VF damage consistent with RNFL damage (nasal step, arcuate field defect, temporal wedge or paracentral/midperiphery depression in clusters of neighbouring test points), VF loss in the upper hemifield that differed from that in the lower hemifield (abnormal glaucoma hemifield test [GHT]) and could not be explained by any other disease, or an open-angle on gonioscopy. Abnormal SAP results were defined as the presence of a cluster of three points with $p < 5\%$, a cluster of two points with $p < 1\%$ on pattern deviation probability plots, or a pattern standard deviation (PSD) with $p < 5\%$ or GHT outside normal limits.

Normal eyes were consecutively recruited from patients referred for refraction who underwent routine examination without abnormal ocular findings, or from hospital staff. Control group participants were required to have intraocular pressure (IOP) < 20 mmHg, no optic disc morphology suspicious for glaucoma, and a normal SAP.

Optic nerve head topography was performed by the same operator with undilated pupils under dim ambient light. The optic disc contour line was drawn along the inner margin of the scleral ring of Elschnig by an experienced investigator (BB). A mean ONH topographic image was automatically obtained from three scans (10° field of view), centred on the optic disc using HRT II, with HRT III software Version 3.0 (Heidelberg Engineering GmbH). Corneal curvature measurements were recorded using keratometry to correct for magnification error. Good image quality was defined as follows: acquisition sensitivity $< 90\%$; topography standard deviation (SD) < 35 mm; $> 75\%$ of the disc within the target circle; minimal movement during the acquisition movie; no floaters over the disc, and good imaging clarity and exposure. Glaucoma probability score analyses that produced only a global result or no results were excluded from the study because the GPS model was only partially compatible or was completely incompatible with the shape of the ONH. Moorfields regression analysis automatically classified the optic disc as 'normal limits' if the observed rim area is within 95% prediction limits and as 'borderline' or 'outside normal limits', if the observed rim area is smaller than 95% or 99.9% prediction limits, respectively, whereas GPS scores of 0–27% were categorized by the software as within normal limits, scores of 28–64% as borderline and scores of 65–100% as outside normal limits. All tests and imaging were carried out within a 2-week period.

Statistics

Data were evaluated using SPSS Version 13.0 (SPSS, Inc., Chicago, IL, USA). Optic nerve head topographic parameters were compared between POAG and control subjects using Student's *t*-test or Mann–Whitney *U*-test. The level of significance was considered as $p < 0.05$. Receiver operating characteristic (ROC) curves were plotted and the areas under the ROC curve (AUC) were calculated for all parameters to assess their usefulness for differentiating glaucomatous eyes from healthy eyes. The diagnostic accuracies of the two classifications were measured when the borderline was taken as normal (highest specificity criteria) or abnormal (highest sensitivity criteria). The MRA for the most abnormal sector Moorfields classification (MFC) result was compared with the global GPS and the agreement between them calculated using the unweighted kappa (κ) coefficient. The strength of agreement with κ-values was interpreted as follows: 0.0 = no agreement; < 0.40 = fair agreement; 0.40–0.59 = moderate agreement; 0.60–0.75 = good agreement; > 0.75–0.99 = excellent agreement, and 1.0 = perfect agreement.

Results

The control group included 61 men and 123 women, with a mean age of 59.6 ± 9.7 years. The POAG group comprised 60 men and 98 women, with a mean age of 63.0 ± 10.7 years. The average VF mean deviation (MD) was − 1.55 ± 1.34 dB in the control group and − 6.97 ± 4.98 dB in the POAG group, whereas average PSD values were 1.79 ± 0.26 dB and 4.28 ± 3.33 dB in the control and POAG groups, respectively. Median HRT SDs were 21 μm in the control group and 27 μm in the glaucoma group. Optic nerve head topographic parameters showed statistically significant differences between the control and POAG groups ($p < 0.001$) (Table 1). The parameters with the highest AUC were global GPS (0.86) (Fig. 1), cup : disc area (0.85), rim : disc area (0.85) and vertical cup : disc (0.85). The cut-off value for the global GPS in the ROC curve that best discriminated between glaucomatous and normal eyes was 0.52 (sensitivity, 74%; specificity, 82%). When specificity was determined as 90%, the cut-off value for the GPS was 0.64, with a sensitivity of 66%.

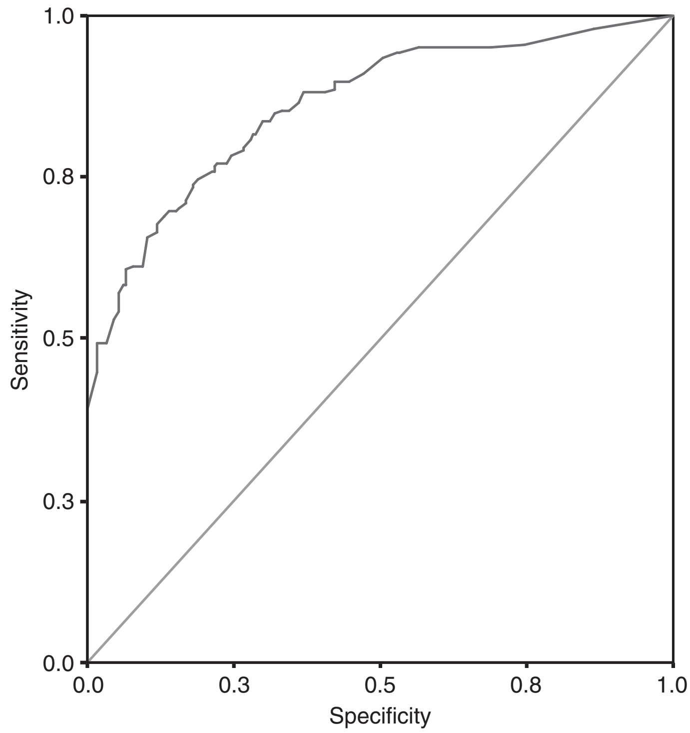

Fig. 1. Area under the receiver operating characteristic curve for glaucoma probability score.

The classification of optic discs according to the MRA and GPS algorithms is given in detail in Table 2. According to highest specificity criteria, MRA had a sensitivity of 67.7% and a specificity of 95.1%, whereas the GPS had a sensitivity of 70.9% and a specificity of 88.0%. According to highest sensitivity criteria, MRA had a sensitivity of 81.0% and a specificity of 75.0%, whereas the GPS had a sensitivity of 89.2% and a specificity of 57.6%. A moderate agreement of 68% (233 eyes) with a κ coefficient of 0.51 was found between MRA and the GPS (Table 3).

Table 1. Comparison of Heidelberg Retina Tomograph parameters between primary open-angle glaucoma and control subjects.

Parameters	Control group	POAG group	p-value	AUC	Cut-off, sensitivity (specificity 90%)
Disc area, mm^2	1.94 ± 0.4	2.2 ± 0.5	< 0.001	0.66	2.37, 28%
Cup area, mm^2	0.47 ± 0.28	1 ± 0.47	< 0.001	0.83	0.82, 63%
Rim area, mm^2	1.47 ± 0.23	1.2 ± 0.36	< 0.001	0.76	1.2, 54%
Cup : disc area	0.23 ± 0.11	0.44 ± 0.16	< 0.001	0.85	0.38, 66%
Rim : disc area	0.77 ± 0.11	0.56 ± 0.16	< 0.001	0.85	0.63, 66%
Cup volume, mm^3	0.11 ± 0.1	0.31 ± 0.24	< 0.001	0.8	0.27, 50%
Rim volume, mm^3	0.39 ± 0.13	0.27 ± 0.14	< 0.001	0.76	0.25, 48%
Mean cup depth, mm	0.22 ± 0.09	0.32 ± 0.11	< 0.001	0.77	0.34, 45%
Max cup depth, mm	0.61 ± 0.21	0.74 ± 0.18	< 0.001	0.67	0.89, 22%
Vertical cup : disc	0.35 ± 0.21	0.61 ± 0.17	< 0.001	0.85	0.59, 66%
Height variation contour, mm	0.39 ± 0.1	0.36 ± 0.1	< 0.001	0.61	0.29, 28%
Cup shape	− 0.2 ± 0.07	− 0.11 ± 0.08	< 0.001	0.81	− 0.11, 52%
Mean RNFL thickness, mm	0.26 ± 0.06	0.2 ± 0.07	< 0.001	0.74	0.18, 38%
Cup depth	0.61 ± 0.18	0.68 ± 0.15	< 0.001	0.62	0.84, 17%
HRNFL curvature	− 0.01 ± 0.03	− 0.07 ± 0.05	< 0.001	0.85	− 0.05, 67%
VRNFL curvature	− 0.1 ± 0.05	− 0.14 ± 0.05	< 0.001	0.72	− 0.18, 25%
GPS	0.28 ± 0.22	0.68 ± 0.26	< 0.001	0.86	0.64, 66%
Rim steepness	− 0.17 ± 0.49	− 0.37 ± 0.43	< 0.001	0.63	− 0.77, 14%
Cup size	0.38 ± 0.16	0.58 ± 0.29	< 0.001	0.74	0.61, 44%

POAG = primary open-angle glaucoma; AUC = area under the curve; RNFL = retinal nerve fibre layer; HRNFL = horizontal retinal nerve fibre layer; VRNFL = vertical retinal nerve fibre layer; GPS = glaucoma probability score.

Discussion

Confocal scanning laser ophthalmoscopy has become an important tool in detecting structural damage to the ONH and RNFL and in identifying glaucoma progression (Miglior et al. 2001; Zangwill et al. 2001; De León-Ortega et al. 2006; Saarela & Airaksinen 2008). HRT III software takes advantage of an enlarged, race-specific database and a machine-learning classifier to help better identify glaucoma. In this study, we assessed the diagnostic accuracy of this new software in differentiating glaucomatous eyes from normal eyes in a Turkish population and evaluated the agreement between its two algorithms, MRA and the GPS, in classifying an eye as glaucomatous or not. Moorfields regression analysis is a linear regression that compares a subject's rim area with the predicted rim area for a given disc area and age and its results are based on confidence limits of the regression analysis derived from a normative database. As far as HRT II criteria go, MRA had already been considered to represent the most efficient criteria

Table 2. Classification of optic discs according to Moorfields regression analysis (MRA) and glaucoma probability score (GPS) in control and primary open-angle glaucoma (POAG) subjects.

	MRA		GPS	
	Control group (%)	POAG group (%)	Control group (%)	POAG group (%)
Normal	138 (75)	30 (19)	106 (57.6)	17 (10.75)
Borderline	37 (20.1)	21 (13.3)	56 (30.4)	29 (18.35)
Abnormal	9 (4.9)	107 (67.7)	22 (12)	112 (70.9)

Table 3. Agreement between the classification results of Moorfields regression analysis (MRA) and glaucoma probability score (GPS) within the whole study population.

		GPS		
		Normal (%)	Borderline (%)	Abnormal (%)
MRA	Normal	109 (31.9)	37 (10.8)	22 (6.4)
	Borderline	12 (3.5)	29 (8.5)	17 (5.0)
	Abnormal	2 (0.6)	19 (5.6)	95 (27.8)

for open-angle glaucoma diagnosis (Miglior et al. 2003). The GPS provides a disease probability value based on the three-dimensional shape of the optic disc and peripapillary RNFL. The GPS is an automated approach to ONH analysis that eliminates the operator-dependent factor and is therefore expected to have better diagnostic accuracy than MRA. In the present investigation, the diagnostic precision of a large number of parameters was evaluated with the area under ROC curves, sensitivities and specificities. All ONH topographic parameters differed significantly between glaucomatous and healthy eyes. Mean global GPS was 0.28 in the control group and 0.68 in glaucomatous eyes. Global GPS had the highest AUC (0.86), with a sensitivity of 74% and a specificity of 82% at a cut-off value of 52, and cup : disc area, rim : disc area and vertical cup : disc had an AUC of 0.85. Ferreras et al. (2007) found global GPS mean scores of 0.24 and 0.62 in their control and glaucoma groups, respectively, with a cut-off value of 51. In another study, Ferreras et al. (2008) observed the highest AUCs in the cup : disc area, rim : disc area and vertical cup : disc parameters (0.94 for all) and showed that global GPS had a sensitivity of 84.4% and a specificity of 74.1% at a cut-off value of 47. Badalà et al. (2007) showed that the cup : disc area and rim : disc area had the largest AUC (0.91 ± 0.03) with HRT III. In a study by De León-Ortega et al. (2007), AUC (sensitivity at 95% specificity) was 0.85 for vertical cup : disc and 0.81 for GPS at the temporal sector. Moreno-Montañés et al. (2008) found an AUC for GPS of 0.77 and put the cut-off value that best discriminated between glaucomatous and normal eyes at 0.70 (sensitivity, 66.26%; specificity, 77.96%).

We used the normative database for White European subjects when analysing the HRT III parameters. In Turkish subjects, we found the mean optic disc area to be 1.94 mm^2 in the control group and 2.20 mm^2 in the glaucoma group. In a Spanish population, optic disc sizes in healthy and glaucoma subjects were found to be 2.10 mm^2 and 2.11 mm^2, respectively, in a study by Moreno-Montañés et al. (2008), and 2.04 mm^2 and 2.16 mm^2, respectively, in Ferreras et al. (2007). In an Italian population, Miglior et al. (2003) found optic disc sizes in healthy and glaucoma subjects of 1.81 mm^2 and 2.04 mm^2, respectively. The mean optic disc size in our control group was between those of the Spanish and Italian populations, whereas the glaucoma subjects had disc sizes comparable with those of both European populations. Therefore, the HRT III European normative database can be used for ONH measurements and analysis in Turkish subjects.

In our study, the mean optic disc area was statistically significantly greater in the glaucoma group compared with the healthy subjects ($p < 0.001$). Disc size is associated with variation of specific anatomical structures of the ONH and RNFL and these disc size-dependent variations may influence susceptibility to glaucoma or the likelihood of glaucoma diagnosis in clinical practice (Hoffmann et al. 2007). Previously, large optic discs were thought to be more prone to glaucomatous damage than small discs (Burk et al. 1992) and various studies have proposed that biomechanical factors such as tensile stress in the ONH represent a primary insult that leads to retinal ganglion cell loss (Bellezza et al. 2000; Sigal et al. 2009). As the optic disc is part of a sphere, a larger disc has a larger inner radius of curvature than a smaller disc, and thus, in a given constant IOP and lamina cribrosa thickness, the larger disc will suffer more tensile stress than the smaller disc (Mehdizadeh & Nowroozzadeh 2008). Thus, a large optic disc could be more susceptible to an IOP rise than a small optic disc. However, Jonas et al. (1991) and Zangwill et al. (2005) were unable to find any association between disc size and development of POAG.

One of the major limitations of this study concerned the difference in disc area between the glaucoma and control groups and its effect on the evaluation of the diagnostic abilities of the HRT parameters because many HRT parameters depend on disc area. That cup area, cup volume and depth may be larger in glaucoma subjects may not only indicate the presence of glaucoma, but may also reflect anatomical differences in disc sizes. However, in this study we also showed that other HRT parameters that do not depend on disc size, such as cup : disc area, rim : disc area and cup shape, differed significantly between the two groups ($p < 0.001$). As patients with parapapillary atrophy were excluded from the study, the findings apply only to a subgroup of glaucomatous eyes without peripapillary alterations.

In classifying the eyes, when we considered eyes with borderline results as normal, the diagnostic abilities of the two algorithms were found to be similar, with a sensitivity of 67.6% and a specificity of 95.1% for MRA, and a sensitivity of 70.9% and a specificity of 88.0% for the GPS. Harizman et al. (2006) showed that global GPS achieved sensitivity and specificity of 77.1% and 90.3%, compared with 71.4% and 91.9% for the overall MRA classification, when MRA sectors outside the 99.9% confidence interval limits (outside normal limits) and GPS values > 0.64 were considered abnormal. In a study by Coops et al. (2006), the sensitivity and specificity of the GPS and MRA were 59% and 91%, and 56% and 87%, respectively. Zelefsky et al. (2006) found the sensitivity and specificity of HRT III MRA analysis to be 81.3% and 93.8%, respectively, in White subjects and 65.4% and 90.3%, respectively, in Black subjects after adjustment for race. In Moreno-Montañés et al. (2008), MRA sensitivity and specificity were found to be 39.8% and 93.2%, respectively, and GPS sensitivity and specificity were reported as 71.1% and 69.5%, respectively, according to the most specific criteria.

De León-Ortega et al. (2007), using the highest sensitivity criteria and classifying borderline results as abnormal, found the sensitivities of MRA III and GPS to be 79% and 74%, respectively, and the specificities of MRA III and GPS to be 76% and 58%, respectively, in a European group. Using the same criteria, we found MRA and GPS sensitivities of 81.0% and 89.2%, respectively, and specificities of 75.0% and 57.6%, respectively, in a Turkish population, which means that the GPS had a high false-positive rate and classified approximately half the normal eyes as abnormal. Moreno-Montañés et al. (2008) showed that MRA sensitivity and specificity were 68.7% and 83.1%, respectively, whereas GPS sensitivity and specificity were 85.5% and 54.2%, respectively, according to the highest sensitivity criteria. Ford et al. (2003) found the sensitivity and specificity of MRA to be 78% and 81%, respectively, using the same criteria. In the study by Ferreras et al. (2008), the best sensitivity and specificity pairs for the HRT classifications were 84.4% and 83.8%, respectively, for overall MRA, and 93.3% and 58.0%, respectively, for global colour-coded GPS.

Another limitation of this study was that the glaucoma patients were pre-selected according to the clinical diagnosis of the examiner based on ONH findings and/or abnormal VF test results. We did not include glaucoma suspects or pre-perimetric glaucoma patients with an ONH of normal appearance. Our study, therefore, assessed whether HRT distinguished glaucoma patients from normal subjects similarly to our method of pre-selecting glaucoma patients. Differences in sensitivity and specificity values among studies may be explained by the variable criteria used to define glaucoma and differences in the distribution of glaucoma subjects according to severity of disease.

This study shows that newer software does not always enhance the diagnostic abilities of a device. However, the GPS software may help operators who are inexperienced in defining the borders of the disc to analyse the ONH parameters automatically without having to draw the contour line manually.

In our study, an agreement between MRA and GPS was found in 68% of cases, with a κ coefficient of 0.51. Moreno-Montañés et al. (2008) reported a lower agreement of 56.6% with a κ coefficient of 0.34, whereas Burgansky-Eliash et al. (2007) and Coops et al. (2006) reported agreements of 78.5% (κ = 0.56) and 71% (κ = 0.52), respectively, which were very close to our findings. Moreno-Montañés et al. (2008) explained this discrepancy as indicative of the fact that their study group included a large number of eyes with early glaucoma. It is interesting to find only a moderate agreement between the two software programs within the same device in many studies. However, they analyse different features of the optic disc: MRA compares the subject's rim area with the predicted rim area for a given disc area and age based on a reference plane, whereas the GPS estimates the probability of glaucomatous damage based on horizontal and vertical RNFL curvature and three measures of ONH shape (cup size, cup depth and rim steepness).

In conclusion, the GPS automated classification showed similar sensitivity to MRA classification, but considerably lower specificity, and the level of agreement between the GPS and MRA in the classification of eyes as normal or abnormal was moderate. Our results suggest that the GPS may be a valuable algorithm for glaucoma detection and screening which does not require operator-dependent contour line placement. However, further studies are needed to determine the limitations of this new algorithm.

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