

The Impact of Definition of Primary Open-angle Glaucoma on the Cross-sectional Assessment of Diagnostic Validity of Heidelberg Retinal Tomography

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- **PURPOSE:** To evaluate the impact of different definitions of primary open angle glaucoma (POAG) on assessment of the diagnostic validity of Heidelberg Retinal Tomography (HRT).
- **DESIGN:** Retrospective, cross-sectional study.
- **METHODS:** A search of MEDLINE (1992–2003) led to the retrieval of 181 papers containing definitions of POAG, including the eight visual field (VF)-based definitions used for this study. A sample of 193 normal subjects, 222 patients with suspected POAG, and 103 with POAG underwent HRT and the 24 II Humphrey VF examinations to assess the diagnostic validity of HRT. POAG was defined on the basis of Glaucoma Hemifield Test (GHT) “out of normal limits” associated with corrected pattern standard deviation (CPSD) > 2 dB and intraocular pressure (IOP) \geq 22 mm Hg. The VFs were re-analyzed and categorized according to the other eight definitions of POAG: IOP formed part of all the definitions, whereas the appearance of the optic disk did not. The sensitivity and specificity of each scenario were calculated by standard procedures.
- **RESULTS:** The definitions of POAG found in the literature included 17 IOP criteria, more than 15 optic disk criteria, and more than 30 VF criteria. The sensitivity of HRT ranged from 0.51 to 0.80, and its specificity from 0.94 and 0.95 when the patients with suspected POAG were excluded; diagnostic validity was

much lower and still variable when the POAG suspects were included with the normal or the POAG groups.

- **CONCLUSIONS:** The most commonly used VF-based definitions of POAG led to substantial differences in the sensitivity and specificity of HRT when using the same large sample of normal subjects and POAG patients. A standard definition of POAG is needed to make diagnostic investigations more accurate and comparable. (Am J Ophthalmol 2005;139:878–887. © 2005 by Elsevier Inc. All rights reserved.)

PRIMARY OPEN-ANGLE GLAUCOMA (POAG), WHICH IS one of the major causes of blindness in the world, involves the progressive loss of retinal ganglion cells and subsequent visual field (VF) damage. The loss of retinal ganglion cells is clinically detectable as a structural modification of the optic disk or as a loss of retinal nerve fiber layer reflectivity, particularly when using a blue or green light.^{1,2} As the optic disk and RNFL are usually evaluated by subjective techniques (ophthalmoscopy, retinography, and so on), which are clearly based on the examiner’s experience, it may be useful to introduce objective quantitative measurements that should improve the ability to discriminate normal from abnormal (glaucomatous) conditions.

Over the last few years, a number of new devices have been developed for this purpose: some provide quantitative measures of a variety of optic disk parameters,^{3,4} whereas others are designed to measure only the thickness of RNFL^{5,6} or the whole retina.⁷

The Heidelberg Retina Tomograph (HRT) has been widely investigated to assess the reproducibility of topographic measures^{3,8–12} and their clinical validity in differentiating normal from glaucomatous optic disks, but the results are very different in terms of sensitivity and specificity^{13–21} for a number of reasons. First, the fact that the optic disk shapes and sizes vary widely in the normal

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population and that there is a close correlation between disk, rim, and cup sizes^{22,23} may negatively affect the use of one or more standard HRT parameters as a means of differentiating normal and glaucomatous optic disks.¹⁴ Second, the HRT stereometric parameters depend on the position of the reference plane along the “z” axis, which, as it is based on anatomic investigations,^{23,24} is variable and unpredictable.¹⁹ Finally, the different studies used different VF criteria as well as different intraocular pressure (IOP) cutoff values to define “glaucoma.”

The software implemented in the HRT II includes the Moorfields Regression Analysis (MRA), which is highly capable of discriminating normal and glaucomatous patients on the basis of a comparison between the examined optic disk and a dedicated database of normal eyes.^{17,20,21} The advantage of the MRA is that it uses the global and sectorial rim area adjusted for disk size and age, which is believed to improve the specificity of the examination.

The aim of this study was to evaluate the impact of different definitions of POAG on the cross-sectional assessment of HRT examination of the optic disk by assessing the sensitivity and the specificity of HRT-MRA in detecting glaucomatous visual field changes. The study population included a large sample of healthy subjects, patients with ocular hypertension (OHT) who are at higher risk of developing glaucoma, and POAG patients representative of the population in our clinical settings.

METHODS

THIS RETROSPECTIVE STUDY IS BASED ON A TWO-STEP procedure: the first (a review of the literature) involved searching for and establishing the distribution of the definitions of POAG in cross-sectional studies of new tools for the diagnosis of POAG published in English over the last 12 years; the second (clinical evaluation) was based on applying the most commonly used definitions of POAG (as gold standard) to a large sample of normal and glaucomatous patients evaluated by means of HRT.

• **REVIEW OF THE LITERATURE:** A detailed search on MEDLINE (January 1992–December 2003) was made using the following key words: glaucoma, Heidelberg Retina Tomograph (HRT), Optical Coherence Tomography (OCT), Laser Scanning Polarimetry-Nerve Fiber Analyzer (GDx), Retinal Thickness Analyzer (RTA), Scanning Laser Ophthalmoscopy (SLO), Frequency Doubling Technology (FDT), and Short Wavelength Automated Perimetry (SWAP).

Editorials, longitudinal studies, and reviews were not considered. Of the 210 retrieved papers, 29 were excluded: 13 did not give a detailed definition of POAG, 8 were restricted to low-tension glaucoma (LTG), and 8 were strictly technical studies often not involving POAG.

The remaining 181 papers were analyzed and classified on the basis of the three most quoted parameters: IOP, VF, and optic nerve head appearance (ONH). At the end of this process, we arbitrarily identified a limited number of definitions of POAG (including most of those used in the literature), to be used during the second phase of the investigation.

• **CLINICAL EVALUATION:** The definitions of POAG were used as “gold standards” to assess the clinical validity of HRT in identifying glaucoma in a sample of normal subjects, POAG patients, and patients with suspected POAG. To simplify the investigation, we arbitrarily used the same IOP criterion (> 21 mm Hg) and did not include the ONH evaluation to avoid any evaluation bias as the HRT only evaluates the optic disk. The only variable consisted of the criteria used to define a normal/abnormal VF.

The VF-based definitions were then applied to the study population, which consisted of 518 patients aged 25 to 81, attending the Glaucoma or Outpatient Services at S. Paolo Hospital in Milan during a time frame of approximately 12 months. The study entry criteria had to be fulfilled in both eyes, and one eye was randomly chosen for each subject. Our Institutional Review Board was informed about the protocol and ruled that no consent was needed because this was a retrospective chart review of data normally obtained in clinical practice. The inclusion criteria were 20/20 visual acuity, a clear lens, and a normal retina; the exclusion criteria were myopia > -6 diopters, hyperopia > 4 diopters, optic disk abnormality (i.e., drusen or a tilted disk), a history of neurophthalmologic diseases, a diagnosis of LTG, and HRT images of poor quality (mean images with a standard deviation > 40 μ m). All of the patients included in the study underwent a complete ophthalmologic evaluation: biomicroscopy of the anterior segment and IOP measurements by Goldman tonometry were made before pupillary dilation; VF examination by the Humphrey 750 DS 24 II program (Zeiss, San Leandro, California, USA). Last VF performed by the participants was used for the purposes of the study. Unreliable VF was not considered for the study, and patients not correctly performing the VF (e.g., showing a clear learning effect) were not included in the study. The indirect ophthalmoscopic evaluation and HRT examination were carried out in mydriasis.

The normal subjects had an IOP of < 22 mm Hg and a normal VF. Their (GHT) results were “within normal limits” and they had a (CPSD) of ≤ 2 dB. These subjects were randomly enrolled from the Outpatient Service of our Institution to collect a large database of “HRT examinations” from a population with normal IOP and normal VF to be used for scientific purposes.

POAG was defined as the presence of an abnormal VF consistent with glaucoma and a history of IOP of ≥ 22 mm Hg (without topical medical treatment). The “glaucoma-

tous" VF was defined on the basis of "outside normal limits" GHT results and a statistically significant CPSD of >2 dB.^{21,25} The VF defects had to be present in two different VFs within a time span of 6 months. The last visual field was used in determining the subject's category. The clinical appearance of the optic disk was used to exclude patients with particular patterns such as the presence of drusen or tilted disk but was not considered when classifying the subjects.

The definition of patients with suspected POAG was based on the presence of an IOP of ≥ 22 mm Hg without therapy and a normal VF. However, for the purposes of the study, this group also included all of the patients with an IOP of ≥ 22 mm Hg, "borderline" or "outside normal limits" GHT results, and a CPSD ≤ 2 dB, or "within normal limits" GHT results and a CPSD of >2 dB.

POAG patients and patients with suspected POAG were consecutive cases attending the Glaucoma Service of our Institution who systematically underwent IOP measurement, VF and HRT examinations, and who were checked for the use of any ocular hypotensive medication. Most of them already had several VF performed; for those who were attending the Glaucoma Service for the first time, a repetition of the VF was performed shortly after.

At the time of the study, IOP was < 22 mm Hg (under topical medical treatment) in the patients with POAG or suspected POAG to avoid a possible bias in the HRT evaluation induced by moderate differences in IOP in the three groups.²⁶

The HRT (Heidelberg Instruments, Heidelberg, Germany) is a confocal scanning laser ophthalmoscope that uses a diode laser (wavelength, 670 nm) to scan the retinal surface in three dimensions. A topographic image is usually taken as a series of 32 confocal images (i.e., 32 optical sections) on 32 consecutive focal planes, each consisting of 256×256 pixels. The HRT examinations were performed using a 10-degree angle view.

Three topographic images were obtained for each eye, and a mean topographic image was analyzed using version 2.01 software. The optic margin was delimited by a contour line placed around the inner edge of Elschnig ring by two clinicians whose reproducibility has been previously evaluated,¹² and the operating software provided 12 predefined shape parameters. For this analysis, the reference plane was set at the standard value of $50 \mu\text{m}$ below the mean retinal surface at the temporal sector between 350 degrees and 356 degrees.

The HRT classification of the optic disk was determined according to Wollstein and associates (1998).¹⁷ The MRA classification is based on 112 normal white Caucasian eyes and 77 early glaucomatous white Caucasian eyes. MRA takes into account the global and sectorial rim area corrected for global and sectorial disk area and uses three grades of classification: "normal" if all of the measurements fall within the 95% confidence intervals (CI); "borderline" if at least one falls between the lower 95% and 99.9% CI;

and "outside normal limits" if at least one rim area measurement is less than the lower 99.9% CI. To obtain data that could be adequately compared with those provided by Wollstein and associates (1998), the cases defined as borderline were considered normal. The MRA is not implemented in the standard software of the HRT I but is available as an add-on program; it was provided to the authors by Heidelberg Engineering.

Three different analyses were made. In analysis 1, the patients with suspected POAG were excluded. In analysis 2, the normal patients and those with suspected POAG were put in the same group. In analysis 3, the patients with known and suspected POAG were put in the same "POAG group."

Sensitivity and specificity were calculated according to standard procedures. An independent two-tailed *t* test was used to compare mean values between two groups. The one-way ANOVA test was used to compare means among groups. The chi-square test was used to test homogeneity of sensitivity and specificity with the different definitions of POAG.

RESULTS

• **REVIEW OF THE LITERATURE:** There was a large variety of definitions of POAG and a wide range of cutoff of all three parameters, IOP, optic disk, and VF, considered for this purpose.

The IOP cutoff values in the definition of POAG varied from >18 mm Hg to >35 mm Hg (Figure 1).

Most of the ONH criteria included in the POAG definition were based on clinical assessments of the following optic disk features: the presence of a localized loss of neuroretinal rim (notch), thinning of the neuroretinal rim, generalized loss of optic rim tissue, cup-to-disk asymmetry, nerve cupping, nerve fiber layer defects or peripapillary hemorrhages, and so on. We pooled these criteria in a single "clinical definition" of the ONH. Other studies also included semiquantitative assessments such as a vertical or horizontal cup-to-disk (C/D) ratio > 0.3 , C/D ratios asymmetry between two eyes > 0.2 , or vertical C/D ratio > 0.6 . We arbitrarily assigned these criteria to "C/D." In the case that both qualitative and semiquantitative criteria were included, our classification was "C/D + clinical" (Figure 2). Overall, more than 15 subjective or semiquantitative criteria were counted.

VF showed a high variability in cutoff between normal and abnormal subjects (Figure 3). Different parameters of the VF printout were used to define glaucomatous VF, but many studies included "nonspecific clinical" criteria (such as "visual field with glaucomatous changes" or "the presence of nasal step"). Overall, more than 30 different criteria were counted.

The following definitions of POAG were considered (some represent a series of similar definitions using the

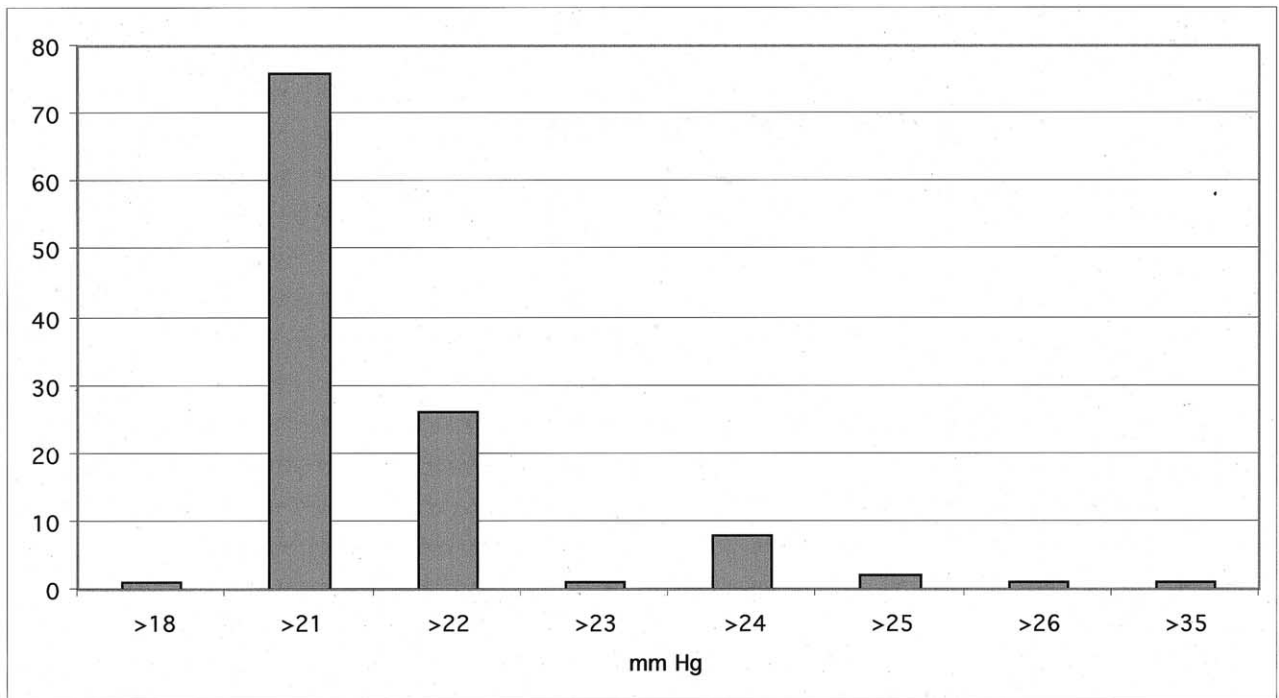


FIGURE 1. Distribution of IOP cutoff values included in the definition of POAG, which were reported in the 181 papers retrieved from MEDLINE (1992–2003). In 65 papers there was no IOP-based definition of POAG.

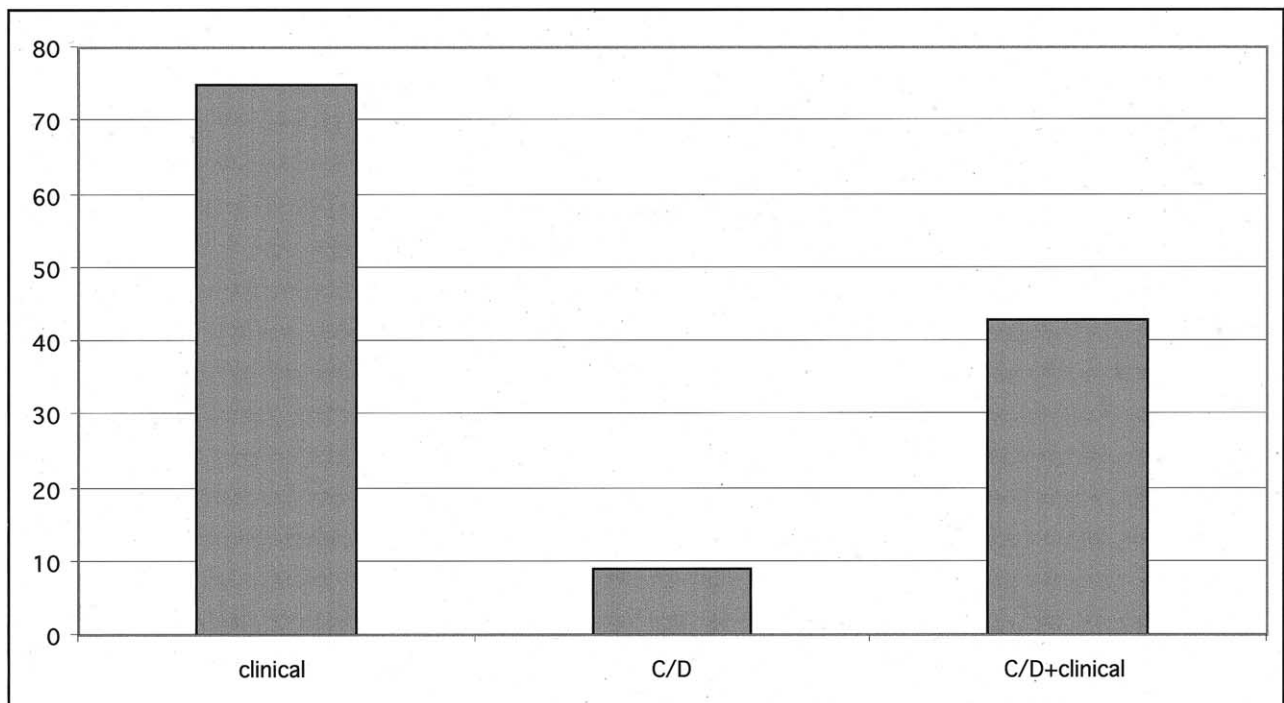


FIGURE 2. Distribution of the criteria used to define optic nerve head changes included in the definition of POAG, which were reported in the 181 papers retrieved from MEDLINE (1992–2003). In 54 papers there was no OD-based definition of POAG. Clinical = subjective clinical judgment, including “the presence of a localized loss of neuroretinal rim (notch),” “thinning of the neuroretinal rim,” “generalized loss of optic rim tissue,” “cup-to-disk asymmetry,” “nerve cupping,” “nerve fiber layer defects,” or “peripapillary hemorrhages.” C/D = cup/disk.

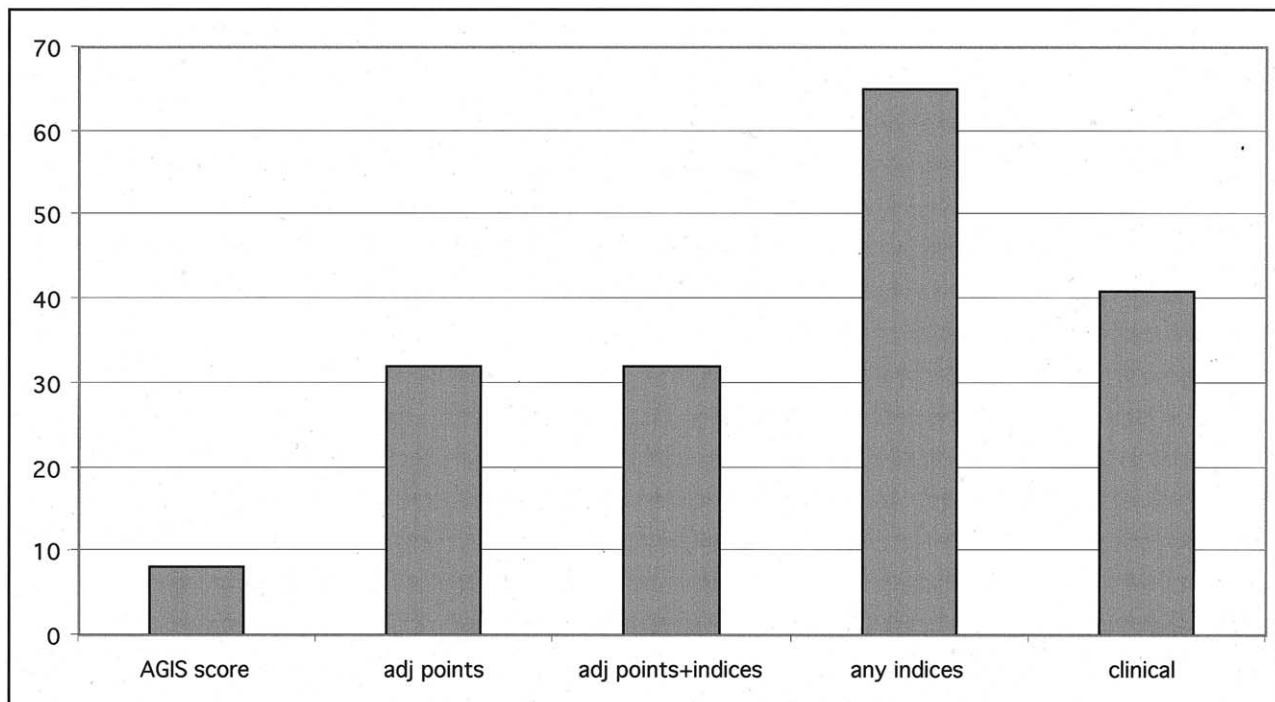


FIGURE 3. Distribution of the criteria used to define visual field changes included in the definition of POAG, which were reported in the 181 papers retrieved from MEDLINE (1992–2003). In three papers there was no VF-based definition of POAG. AGIS score = Advanced Glaucoma Intervention Study score. Adj points = adjacent points. Clinical = subjective clinical judgment, including “visual field with glaucomatous changes” or “the presence of nasal step.”

same parameters with slightly different cutoff values). This decision was taken to make the investigation more simple and to summarize often redundant criteria, which take into account the same VF parameters but different threshold values.

(1) AGIS score: the Advanced Glaucoma Intervention Study (AGIS) is a multicenter, randomized clinical trial. The investigators developed quantitative methods to assess the reliability and measure the severity of glaucomatous VF defects using the 24–2 threshold program of the Humphrey Visual Field Analyzer. The assessment of the reliability of automated VF tests was based on the number of questions asked, the percentage of fixation losses, false-positive responses, and false-negative responses, and the degree of short-term fluctuations. The AGIS VF defect score is based on the number and depth of clusters of adjacent depressed test sites in the upper and lower hemifields and in the nasal area of the total deviation printout of the threshold program single-field test STAT-PAC-2 analysis. The score ranges from 0 (no defect) to 20 (all test sites deeply depressed).²⁷

(2) Adjacent points criteria: VF damage was indicated by: (1) at least three adjacent points depressed by 5 dB or more in comparison with age-corrected normal values; or (2) at least two adjacent points depressed by 5 dB or more in comparison with age-corrected normal values, with one of these two points deviating by more than 10 dB; or (3) a

10 dB difference across the nasal horizontal meridian at two adjacent locations.

- (3) Adjacent points + “out of normal limits” GHT.
- (4) Adjacent points + CPSD >2 dB.
- (5) Adjacent points + mean deviation < -2 dB.
- (6) MD < -2 dB.
- (7) GHT “out of normal limits.”
- (8) CPSD > 2 dB.

When applying each of the eight different criteria, the normal individuals were classified on the basis of a normal VF (in the case of the AGIS score criterion, the score was 0) and an IOP < 22 mm Hg. The patients with suspected POAG were classified on the basis of a normal VF and an IOP ≥ 22 mm Hg. A reclassification into a group of LTG was possible if the VF was abnormal, and the IOP was < 22 mm Hg.

• **CLINICAL EVALUATION:** Of the 518 patients included in the study, 193 were normal, 222 had suspected POAG including 180 patients with normal CPSD and GHT results, 9 OHT patients with borderline GHT and normal CPSD, and 33 OHT patients with abnormal GHT or CPSD, and 103 had POAG confirmed on the basis of our criteria. The mean age in the normal, POAG suspect and POAG groups was respectively 56.8 ± 11.2 , 61.2 ± 12.3 , and 67.8 ± 12.3 years, and the mean refraction respectively 0.2 ± 1.6 , 0.1 ± 2.2 , and -0.1 ± 1.8 . The difference in age among the three groups was statistically significant

TABLE 1. Mean (SD) Values of Visual Field Indices and HRT Parameters in Normal Subjects, Patients With Suspected POAG, and POAG Patients

	Normal	Suspected POAG	POAG	P
IOP	16.34 (1.26)	23.35 (1.85)	24.45 (1.81)	<.001
IOP at time of imaging	16.34 (1.26)	16.62 (1.34)	16.94 (1.37)	<.01
MD	-0.56 (1.48)	-1.13 (2.79)	-9.82 (7.15)	<.01
CPSD	0.82 (0.65)	1.55 (1.05)	7.36 (3.45)	<.001
Disk area	1.81 (0.38)	1.91 (0.43)	2.03 (0.46)	<.001
Cup area	0.45 (0.31)	0.69 (0.46)	1.19 (0.57)	<.01
Cup/disk (C/D) area	0.24 (0.12)	0.33 (0.17)	0.56 (0.21)	<.01
Rim area	1.35 (0.24)	1.21 (0.28)	0.84 (0.34)	<.01
Cup volume	0.09 (0.11)	0.18 (0.17)	0.32 (0.24)	<.01
Rim volume	0.37 (0.13)	0.30 (0.12)	0.16 (0.12)	<.01
Mean cup depth	0.20 (0.08)	0.25 (0.11)	0.28 (0.11)	<.001
Max. cup depth	0.56 (0.20)	0.62 (0.22)	0.61 (0.21)	.012
Cup shape measure	-0.19 (0.07)	-0.15 (0.09)	-0.08 (0.15)	<.01
Height variation contour	0.42 (0.11)	0.39 (0.12)	0.37 (0.13)	<.01
Mean RNFL thickness	0.26 (0.08)	0.23 (0.09)	0.15 (0.08)	<.01
RNFL cross sectional area	1.23 (0.36)	1.11 (0.39)	0.73 (0.39)	<.01

CPSD = corrected pattern standard deviation; IOP = intraocular pressure; MD = mean deviation; POAG = primary open-angle glaucoma; RNFL = retinal nerve fiber layer.

TABLE 2. Distribution of Patients by Case Definition and Visual Field Criteria to Define POAG

	AGIS	Adj Points	Adj Points + MD	Adj Points + CPSD	Adj Points + GHT	MD	CPSD	GHT	CPSD + GHT
Normal	164	188	165	188	188	168	193	193	193
POAG suspect	170	176	240	213	230	164	158	203	222
POAG	155	149	111	117	100	161	167	122	103
LTG	29	5	2	0	0	25	0	0	0

AGIS = Advanced Glaucoma Intervention Study score; Adj points = adjacent points; MD = mean deviation; CPSD = corrected pattern standard deviation; GHT = glaucoma hemifield test; POAG = primary open-angle glaucoma; LTG = low-tension glaucoma.

($P < .01$), but the difference in refraction was not ($P > .05$). The descriptive statistics of the VF indices and HRT parameters are shown in Table 1. ANOVA revealed significant differences in all of these variables among the three groups.

The eight VF-based definitions of POAG were then applied to the study population. The distribution of the 518 participants by POAG definition is shown in Table 2. This Table includes the group of LTG patients because a number of individuals defined as being normal according to our criteria formed a group with VF abnormality and IOP < 22 mm Hg. The distribution varied widely, depending on the nine different criteria used to define POAG, suspected POAG, and normal individuals. The number of normal individuals varied from 193 to 164, the patients with suspected POAG from 240 to 158, the POAG patients from 167 and 100, and the LTG patients from 29 to 0.

In analysis 1 (which excluded the patients with suspected POAG), sensitivity ranged from 0.51 to 0.80 ($P <$

.0001), and specificity from 0.94 to 0.95 ($P = .99$) (Figure 4). In analysis 2 (which included the patients with suspected POAG in the normal group), sensitivity ranged from 0.51 to 0.80 ($P < .0001$) and specificity from 0.83 to 0.87 ($P = .74$) (Figure 5). In analysis 3, (which included the patients with suspected POAG in the POAG group), sensitivity ranged from 0.39 to 0.41 ($P = .99$) and specificity from 0.94 to 0.95 ($P = .99$) (Figure 6).

DISCUSSION

IN PATIENTS WITH POAG, OPTIC NERVE HEAD MODIFICATIONS and retinal nerve fiber loss may precede visual field glaucomatous alterations.^{2,28-35} To plan a therapy designed to preserve visual function for as long as possible, it seems to be clinically appropriate to use instruments capable of detecting glaucomatous alterations, particularly in the early stages of the disease.

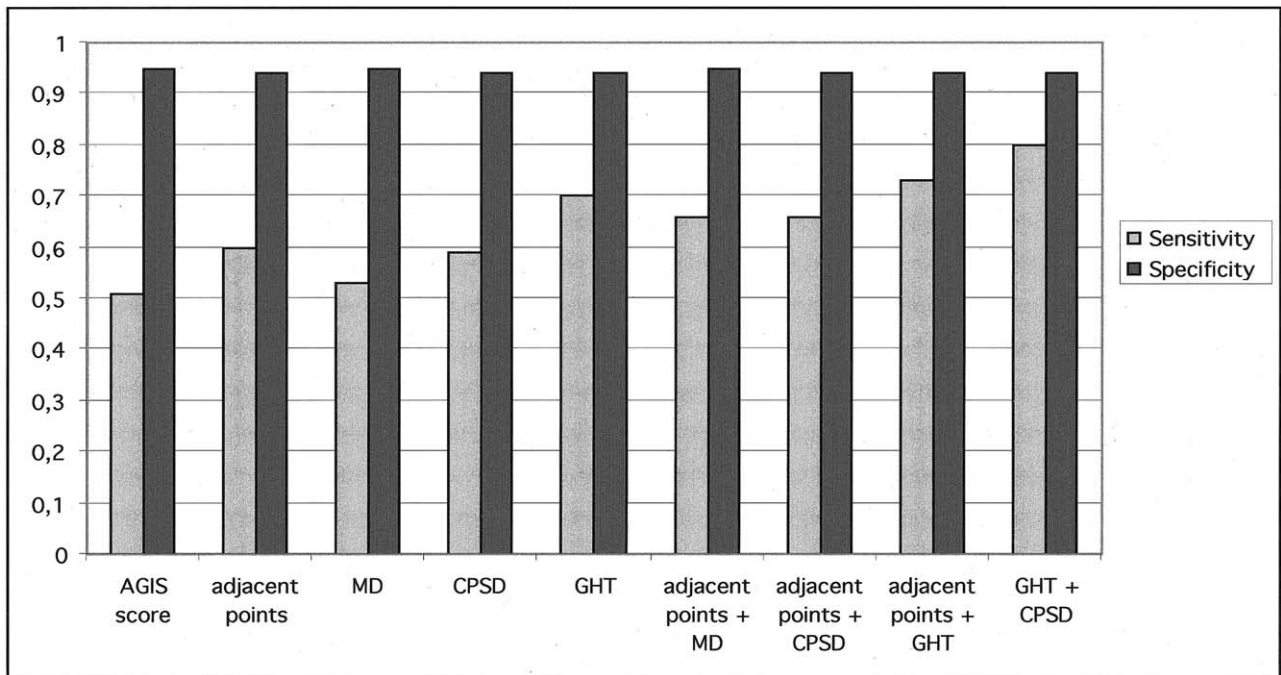


FIGURE 4. Sensitivity and specificity of the Moorfields Regression Analysis of HRT by different “visual field-based” definitions of POAG. In this analysis, the patients with suspected POAG were excluded. AGIS score = Advanced Glaucoma Intervention Study score; MD = mean deviation; CPSD = corrected pattern standard deviation; GHT = glaucoma hemifield test.

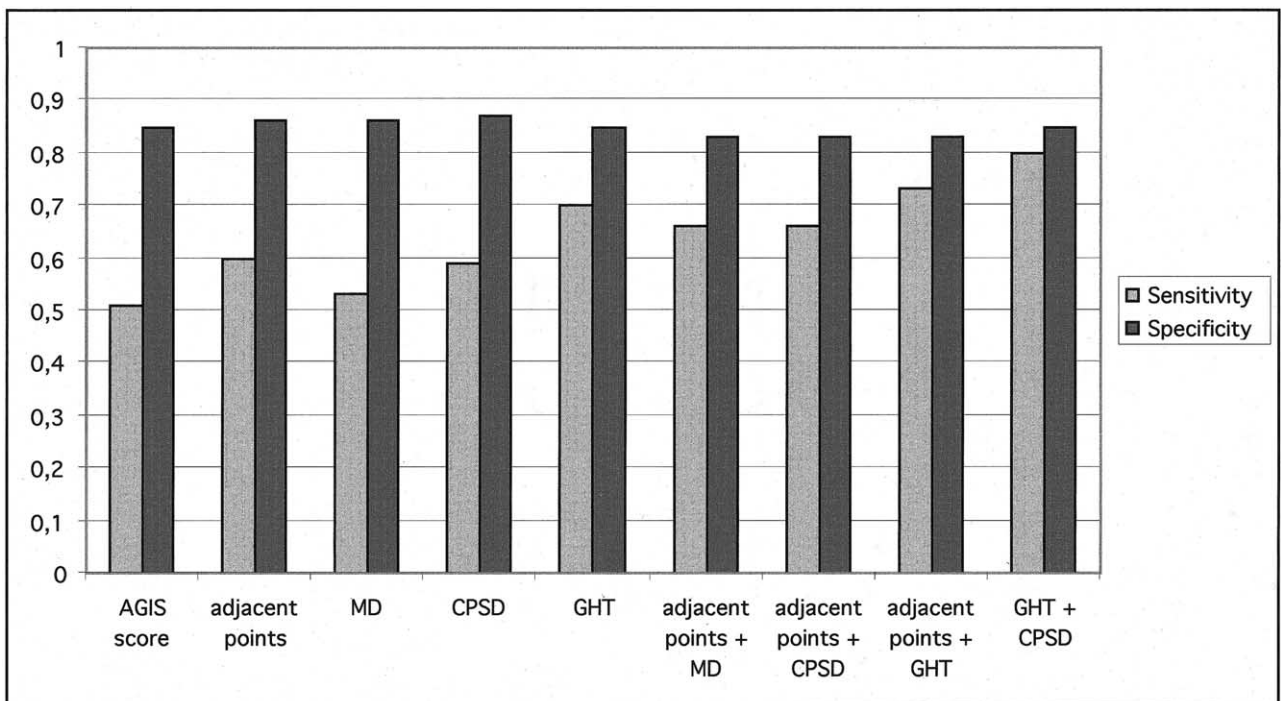


FIGURE 5. Sensitivity and specificity of the Moorfields Regression Analysis of HRT by different “visual field-based” definitions of POAG. In this analysis, the patients with suspected POAG were considered as being “normal.” AGIS score = Advanced Glaucoma Intervention Study score; MD = mean deviation; CPSD = corrected pattern standard deviation; GHT = glaucoma hemifield test.

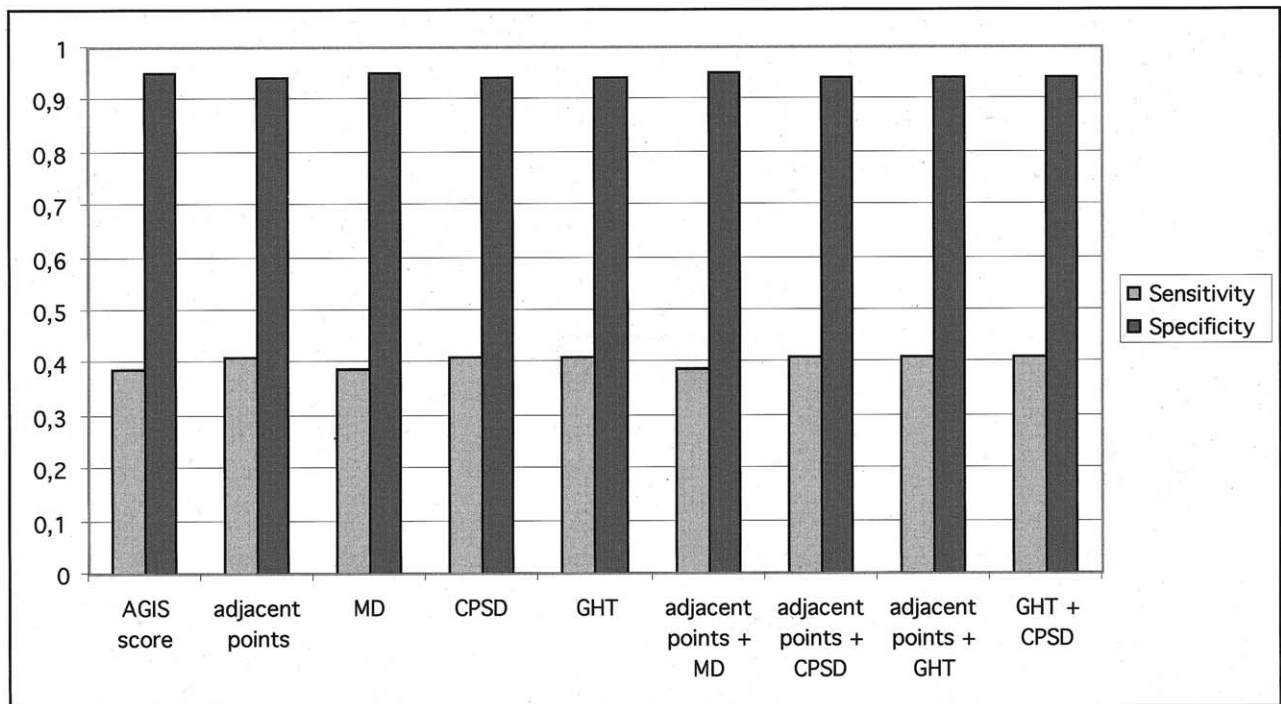


FIGURE 6. Sensitivity and specificity of the Moorfields Regression Analysis of HRT by different “visual field-based” definitions of POAG. In this analysis, the patients with suspected POAG were considered as being “glaucomatous.” AGIS score = Advanced Glaucoma Intervention Study score; MD = mean deviation; CPSD = corrected pattern standard deviation; GHT = glaucoma hemifield test.

A clinically relevant step in the process of assessing new diagnostic methods is to evaluate their diagnostic validity to establish whether they are useful in a clinical setting. We investigated the diagnostic accuracy of HRT in discriminating normal and glaucomatous eyes using different “VF-based” definitions of POAG. A VF-based definition of glaucoma is clinically relevant, because it indicates definite functional loss and it is the “gold standard” of the presence of glaucoma whenever new diagnostic tools are investigated. Moreover, before introducing a new diagnostic method into glaucoma clinical practice, good agreement with the results of a VF test should be demonstrated.³⁴

Our study shows that the definition of POAG used in cross-sectional studies aimed at evaluating the diagnostic validity of various imaging and/or psycho-physical techniques over the last 12 years is extremely variable and inconsistent. The three major parameters included in the POAG definitions were IOP, VF, and optic nerve head appearance. However, there were eight cutoff values for IOP, more than 30 different criteria to define VF loss, and more than 15 different criteria to define glaucomatous optic disk changes in the 181 papers reviewed and many combinations of these criteria. Furthermore, another 13 papers retrieved by MEDLINE did not include any definition of POAG.

Although the criteria used to define optic disk appearance can only be descriptive or semiquantitative and based upon subjective judgment (thus leading to substantial and

expected variability), the criteria used to define IOP and VF should be based on numbers, and, therefore, objective assessments and clear guidelines. It seems that it is not the case.

It is debatable whether IOP should be included in the definition of glaucoma, and there are important examples supporting both points of view. The Early Manifest Glaucoma Trial (EMGT) did not use any IOP cutoff value to separate POAG from LTG but pooled all the OAG patients in the same “pot.”³⁶ The Collaborative Initial Glaucoma Treatment Study (CIGTS) included an IOP ≥ 20 mm Hg or ≥ 27 mm Hg (depending on whether there were any associated VF changes).³⁷ The definition of ocular hypertension in the Ocular Hypertension Treatment Study (OHTS) included only individuals with an IOP ≥ 24 mm Hg in one eye,³⁸ whereas that of the European Glaucoma Prevention Study (EGPS) included only individuals with an IOP ≥ 22 mm Hg in one eye.³⁹ The question as to what IOP cutoff value should be used to distinguish POAG from LTG patients is, therefore, still open, whereas it seems we may still refer to the commonly accepted values of IOP ≥ 22 mm Hg or slightly more in the case of ocular hypertension.

The criterion for defining VF loss in glaucoma (particularly in the early stages) seems to be the crucial issue in defining POAG. The results of our study, which was designed to evaluate the impact of the definition of POAG (using nine different VF criteria) on the assessment of the

diagnostic ability of HRT, clearly point to the heart of the problem. Using the standard parameters of MD, CPSD, GHT, a cluster of adjacent test locations, their combinations, and the AGIS score, the sensitivity of the MRA of the HRT varied from 0.51 - 0.80, whereas the specificity was high and almost stable (ranging from 0.94–0.95). Including subjects with suspected POAG in the normal group led to an overall loss of specificity, which was more or less the same regardless of the definition of POAG; including them in the POAG group led to an overall loss of sensitivity, which tended to be the same whatever POAG definition was used.

The number of individuals classified as being “normal” on the basis of the nine different criteria ranged from 164 to 193 (a difference of 29); the number of individuals classified as having “suspected POAG” ranged from 158 to 240 (a difference of 82); and the number classified as “POAG” (including LTG) ranged from 103 to 186 (a difference of 83). Most of the different reclassifications, therefore, involved the suspected POAG and the POAG groups, and mainly affected the consistency of the “case” classification, as can be seen in the different sensitivity observed when the patients with suspected POAG were excluded from the analysis or were included in the normal group. This may also help to explain why MRA was highly specific using all the nine different definitions of POAG. Such a high degree of specificity may also be interpreted in terms of the robustness of the software in correctly identifying normal optic disks, given the presence of both sectorial and global analysis and the evaluation of rim area as a function of disk area. The same may also explain the apparently higher sensitivity of MRA when the gold standard included the VF global indices that are more indicative of localized loss (such as CPSD and GHT) or the cluster analysis.

The definition of glaucoma may, therefore, have a considerable impact on the evaluation of HRT-MRA aimed at distinguishing normal from glaucomatous subjects, particularly in the early stages of the disease. This is particularly important when we consider that many other factors can affect the appropriate and clinically useful evaluation of the published diagnostic studies: the composition of the sample (the number of cases and controls, the inclusion/exclusion of borderline cases), the source of the patients (referral/not referral centers), any possible bias in the conduct of the study (such as the possible selection bias in the collection of a “normal population”), the ancestry, or case/control matching, and the fact that each single instrument is often evaluated without making any direct comparisons with other methodologies, and so on. For example, the results of a hypothetical diagnostic evaluation of MRA on our studied population could be interpreted totally differently if they had been obtained using the “AGIS score” instead of the “GHT + CPSD analysis” as a gold standard. In the former case, MRA would seem to

be a poor system for identifying glaucoma patients; in the latter case, it would seem to be a good system.

We have ascertained that no standard definition of glaucoma is used in clinical research and can probably hypothesize that no standard and consistent definition of glaucoma is used in clinical practice.

Few previous studies have underlined the importance of the definition of POAG in accurately describing the prevalence of glaucoma in general communities such as Framingham⁴⁰ and Rotterdam.⁴¹ Considerable emphasis has recently been placed on the lack of a standard definition of glaucoma and progressive VF changes indicating glaucoma progression. Bathija and associates (1998) and Lee and associates (1998) reported the inconsistency in the published definitions of POAG and LTG.^{42,43} Katz and associates (1999) showed the absolute inconsistency among the AGIS, EMGT, and CIGTS criteria in identifying the same patients as having progressive diseases.⁴⁴ To the best of our knowledge, ours is the first attempt to evaluate the impact of different POAG definitions on the diagnostic evaluation of an imaging technology such as HRT. On the basis of our results, and the considerable impact of the interpretation of diagnostic investigations on clinical practice, a standard definition of glaucoma or POAG is greatly required and should be used in both clinical investigation and clinical practice to make the comparisons of different technologies more comprehensible and interpretable for the entire ophthalmic community.

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Biosketch

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