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Title:

Diagnostic Accuracy of Imaging Devices in Glaucoma: Meta-Analysis

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Abstract

Imaging devices such as Heidelberg Retinal Tomograph (HRT), scanning laser polarimetry (SLP) and optical coherence tomography (OCT), play an important role in glaucoma diagnosis. **Methods:** A systematic search for evidence-based data was performed. Prospective studies evaluating the diagnostic accuracy of HRT3, GDx and OCT were included. The diagnostic odds ratio (DOR) was calculated. To compare the accuracy among instruments and parameters, a meta-analysis considering the hierarchical summary receiver operating characteristic (H-SROC) model was performed. The risk of bias was assessed using quality assessment of diagnostic accuracy studies (QUADAS-2). Studies in the context of screening programs were used for qualitative analysis. **Results:** 86 manuscripts were included. The DOR values were 29.5 for OCT, 18.6 for GDx and 13.9 for HRT. The heterogeneity analysis demonstrated statistically a significant influence of degree of damage and ethnicity. Studies analyzing patients with earlier glaucoma showed poorer results. The risk of bias was high for patient selection. Screening studies showed lower sensitivity values and similar specificity values when compared to those included in the meta-analysis. **Conclusions:** The classification capabilities of GDx, HRT and OCT were high and similar across the 3 instruments. The highest estimated diagnostic odds ratio was obtained with OCT. Diagnostic accuracy could be overestimated in studies including pre-diagnosed groups of subjects.

Key words: Glaucoma, Biomedical enhancement, Meta-Analysis, Diagnostic Imaging; optic nerve.

1. INTRODUCTION

Glaucoma is the second leading cause of blindness worldwide, (1) and the leading cause of irreversible blindness. (2) It is considered a major public health concern and its prevalence will probably continue to increase as life expectancy continues to rise. In fact, recent work estimates that in 2013 the number of people aged 40-80 years with glaucoma worldwide was 64.5 million and that this number will increase to 76 million in 2020 and 111.8 million in 2040 (3).

Glaucoma describes a group of ocular disorders of multi-factorial etiology. The common clinical feature is characteristic optic neuropathy with potentially progressive, clinically identifiable changes at the optic nerve head (ONH) and the retinal nerve fiber layer (RNFL), comprising focal or generalized thinning of the neuroretinal rim with excavation and enlargement of the optic disc cup, RNFL thinning and a corresponding visual field defect (4). Several studies investigating the structural measurements found substantial evidence that structural changes can develop before the appearance of detectable change in functional measures.(5)(6) These findings together with the demonstrated prognostic value of structural changes, on functional progression, have modified the role of structural measurements in the diagnosis of glaucoma. (7) (8) (9) (10) The World Glaucoma Association has concluded, from evidence and expert consensus, that the diagnosis of glaucoma does no longer require the detection of visual field defects with perimetry, although perimetry is indispensable for documentation and monitoring of functional decline in glaucoma.(7) Ideally, glaucoma diagnostic techniques should identify the majority of patients that require treatment early in the disease course and rule out glaucoma suspects that will not progress to vision loss. Early detection and administration of treatment aim to maintain quality of life by reducing intraocular pressure and visual field progression rate (11).

The identification of structural damage can be performed by direct examination of the fundus and can be complemented by images of the optic disk and different layers of the retina, particularly the retinal

nerve fiber layer (RNFL) and the ganglion cell layer. The role of computerized imaging technologies such as HRT, GDx and OCT (herewith we will refer to them as imaging devices) in glaucoma diagnosis and follow-up has increased in recent years based on the ease of acquisition while offering automated, objective, reliable and accurate quantitative measurements of glaucomatous structural damage (12)(13). These technologies undergo constant evolution, their capabilities improve continuously and they frequently become available before a thorough clinical evaluation has been performed. The aim of this meta-analysis was to estimate the accuracy and detection capability of the most used imaging devices (Scanning Laser Tomography-HRT-; Scanning Laser Polarimetry -GDx- and Optical Coherence Tomography -OCT-) as tools for detection of glaucoma and classification between patients and healthy subjects. Additionally, the results of studies with this objective were compared with those obtained by the same devices in the context of screening programs.

2. METHODS

2.1 Protocol

This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement checklist (14). The protocol is available in <https://www.researchgate.net/publication/296702087> *Protocolo Meta-analisis Dispositivos de Imagen y Retinografia en Glaucoma* (DOI: 10.13140/RG.2.1.1850.8564).

2.2 Study selection criteria

2.2.1 Type of study

All studies published on image devices or laser optical technology (HRT, GDx and OCT) from January 2004 to February 2015 were reviewed. Publications reported in English, Spanish or French were included, but grey literature (posters, communications, and theses) was not taken into account. The included studies

had a prospective design; studies with retrospective selection of cases were accepted only when the clinical application of the study protocol was prospective. Observational, descriptive (base population, cross-sectional), analytical studies (case-control, cohort) and experimental studies (clinical trials) were included in the analysis. Only studies performed to assess classification capabilities of HRT3, GDx VCC/ECC and OCT (Spectral Domain), to differentiate between normal subjects and glaucoma patients in which the index and reference test were used in the same population, were considered. Studies included could have been designed to evaluate the reliability of the instrument if they met all other criteria. Studies evaluating imaging devices in the context of screening programs were also included. Nevertheless, due to the heterogeneity in recruitment methods, subjects included, and clinical settings, screening studies were only considered for a qualitative analysis and to compare the results against those of the meta-analysis.

All studies included evaluated at least one imaging device, with a definition or standard reference diagnosis based on the assessment of the structure and/or visual function and a minimum of 50 participants in the whole sample(15). Studies had to report sensitivity and specificity of the test(s) and also described image quality criteria for the test based on those recommended by the manufacturers of the equipment as being optimal for clinical evaluation.

Studies were excluded if they assessed the ability to diagnose glaucoma of the devices in very specific subgroups of subjects, namely children or young individuals and subjects with ophthalmological or neurological diseases.

2.2.2 Parameters Studied

In order to assess the discriminating capacity of a particular test, the sensitivity and specificity of each test/parameter were considered, as reported by the authors. When several sensitivity values with a

certain specificity cut-off were reported, the cut-off point of 80-85% specificity was chosen. Only parameters which could be obtained with standard commercial software were analyzed, including RNFL thickness around the disk, ONH cup/disk ratio (C/D) and ganglion cell layer/complex thickness. Different studies measured the three innermost retinal layers individually, namely, the RNFL, the ganglion cell layer (RGC) and the inner plexiform layer (IPL). Others combined RGC + IPL and some considered all of them together as the GCC (RNFL+RGC+IPL). In this study only articles calculating GCC, automatically or using algorithms from individual layers data to add them together, were used. GCC scans were centered on the fovea with a diameter of between 6 mm and 9 mm. (see Table 1 for detailed variables). Several clinically used parameters from each instrument were selected for the analysis (Table 1).

2.2.3 Target condition

The target conditioned of interest is manifest glaucoma.

2.2.4 Reference standards

There is no universally-accepted reference standard for the diagnosis of glaucoma. We accepted the definition of glaucoma diagnosis given by study investigators; however we conducted subgroup analyses to assess whether differences between studies could be explained by the choice of the reference standard.

2.3 Sources and electronic search strategy

A systematic search for evidence based on data on imaging devices (January 2004 to February 2015) was performed in Medline and the Cochrane Library. The search was conducted using controlled vocabulary, sensitive descriptors and free text terms (for further information regarding the research scheme see Appendix 1). In addition, a search was similarly performed with sensitive descriptors in scientific ophthalmic journals, namely the Journal of Glaucoma, Investigative Ophthalmology and Visual Science,

American Journal of Ophthalmology, Ophthalmology and British Journal of Ophthalmology, and in the journals included in the Embase database.

2.4 Data collection and analysis

2.4.1 Study Selection

One reviewer (MF) evaluated all study abstracts and classified them as excluded when the information provided in the summary did not meet any of the criteria. They were described as potentially relevant in any other case. Full-text copies of potentially relevant studies were obtained and assessed for a more detailed identification of inclusion criteria. Studies were rigorously revised for eligibility, respecting the required inclusion criteria. Each inclusion criterion had to be fulfilled in the selected study. Failure to comply with a single eligibility criterion was enough to exclude the study from the review.

2.4.2 Data extraction and management

The database of bibliographic records was created with open source software ZOTERO v4.0 (Roy Rosenzweig Center for History and New Media, USA). The reviewer extracted and filed the details of study design, number of participants, index test, comparator and standard reference tests, and outcome data.

2.4.3 Quality assessment

The updated quality assessment of diagnostic accuracy studies, version 2 (QUADAS-2)(16), was used to assess the risk of bias and applicability concerns of all included full-text manuscripts. QUADAS-2 consists of four key domains covering (1) patient selection, (2) index test, (3) reference standard, and (4) flow of patients through the study and timing between index test(s) and reference standard. Each domain was assessed in terms of risk of bias. The first three domains were also assessed for concerns regarding their applicability in terms of whether (i) the participants and setting, (ii) the index test, its conduct or

interpretation, and (iii) the target condition as defined by the reference standard matched the question being addressed by the review (See Table 2 for a description of this evaluation system).

2.4.4 Statistical analysis

All statistical analyses were performed with software SAS 9.3 (SAS Institute Inc., Cary, NC, USA). Experimental units were used to analyze the results reported by each study. They are one outcome of a set of results in the study. These units refer to studies evaluating multiple devices on the same sample. The diagnostic odds ratio (DOR) was calculated for each study. This statistic is a single overall indicator of diagnostic accuracy that indicates how much more frequently (expressed as odds) a positive test result occurs among patients with the condition of interest compared to patients without the condition (17). In order to compare diagnostic accuracy among instruments and among parameters within each instrument, a meta-analysis considering the hierarchical summary receiver operating characteristic (H-SROC) model (18) was performed. This model takes proper account of the sample size regarding diseased and non-diseased cases in each study and allows estimation for random effects and accuracy effects. Results from the H-SROC models were graphically represented using SROC curves. The significance level was set at $p < 0.05$ and 95% confidence intervals (CI) were calculated for sensitivity and specificity. Pairwise comparisons were used considering Tukey's method for correcting type I error in multiplicity contrasts. Forest plots were used to show the sensitivity and specificity of each instrument and study.

2.4.5 Heterogeneity

Forest plots were used to determine evidence of heterogeneity within sensitivity and within specificity. In order to analyze which characteristics could explain this heterogeneity, DOR values were classified in two categories. DOR values were considered low if they were under 18 and high if they were over 18. There is a mathematical relation between the AUC and the DOR of a test.(19) The 18 cut-point was

chosen based on the value of the median DOR in this review (half of the articles had a DOR less than 18 and the other half had a higher DOR). This allows separating the studies into two groups with the same number of observations. The value of 18 corresponded to an AUC of 0.88. Contingency tables and chi-square statistics were used to compare the performance of the tests and the potential influence of different variables including year of publication, ethnicity, quality of the test, reference standard and level of glaucoma.

2.4.6 Screening studies

Studies that assessed the devices in the context of the screening program in risk population were analyzed qualitatively due to the heterogeneity in study design.

2.4.7 Sensitivity analysis

A sensitivity analysis was not performed since most of the studies had a case-control design and only normal and glaucoma cases were used to evaluate the classification capabilities of the imaging devices in this meta-analysis.

3. RESULTS

3.1 Study selection

The electronic searches yielded a total of 8,028 records. Of those, 5,412 titles/abstracts were identified and screened after removal of duplicates. One hundred and fifty seven were deemed potentially relevant for the study objectives and were fully reviewed. Finally, 86 studies met all the inclusion criteria, including 81 for quantitative analysis and 6 for qualitative analysis. One of those fell into both categories (Figure 1).

3.1.1 Study characteristics

A list of full-text papers that were excluded along with the reasons for their exclusion is given in Appendix 2. These reports were excluded because they failed to meet one or more of the inclusion criteria in terms of the study type, number of participants, test, reference standard or outcomes reported. The specific characteristics of each study included, particularly the country where the research took place, the test evaluated, recruitment type, reference standard used, study period, sample enrolled and analyzed, and level of disease severity, are described in Appendix 3. Eighty studies (98.7%) were case control studies and only one was a cohort study. Fifty six studies (69.1%) used visual fields as reference standard and 25 studies (30.9%) used both functional and structural criteria to define glaucoma. In the 81 studies, 54 experimental units evaluated the OCT, 24 assessed the HRT and 25 studied the GDx.

A summary of the characteristics of the studies included in the meta-analysis is shown in Table 3. Fifteen studies were conducted in Korea, 14 in the USA, 10 in Italy, 9 in Spain, 9 in India, 6 in Japan, 4 each in China and Brazil, 3 in Turkey and 1 each in Australia, England, France, Hungary, Netherlands, Sweden and Thailand. One multicenter study was performed in Italy, USA and Argentina, while other multicenter studies took place in Italy, Japan and the USA. The largest study was performed by Sanchez Cano et al. and evaluated the GDx in 451 eyes, whilst the smallest was an OCT study by Fang et al., including 76 eyes. The study period was not reported in 30 papers; the shortest period was 1 month and the longest lasting study, by Coops et al., was performed at the Manchester Royal Eye Hospital from 1998 to 2004 (72 months) and included both a cross-sectional and a longitudinal arm.

3.1.2 Risk of bias

All 81 manuscripts were assessed using the QUADAS-2 tool. The distribution of studies according to the risk of bias in each methodological domain is shown in Figure 2. Patient selection had a high risk of bias

in 49.3% of the studies. Flow and timing domain showed a high risk of bias in 25.9% of the studies. The main reasons for considering this high risk of bias in patient selection were: not enrolling a consecutive sample of participants, not avoiding inappropriate exclusions, and pre-selection of participants. The high risk of bias in the flow and timing was related to an interval of more than 1 month between imaging with the imaging device (index test) and the examination considered as reference standard, and, finally, not including all patients in the analysis. Regarding the index test domain, 44.4% of studies were judged to have a low risk of bias, 6.1% were considered as high risk of bias and in 49.3% the risk was considered to be unclear. The main element causing the high risk of bias in this domain was the not-blind interpretation of the reference standard test and the results of the index test. Additionally, all the studies included were judged to have low concerns for applicability regarding patient selection, index test and target condition as defined by the reference standard. Finally, all studies were considered to match the question being addressed by the review.

3.2 Quantitative Findings: Accuracy of test parameters and image quality

Eighty-one studies reported sensitivity values of the selected parameters obtained at given specificity values, mainly at 0.80 and 0.90. Sensitivities were very heterogeneous (see forest plots; Figures 3, 5 and 7). For the purpose of this meta-analysis we will present the accuracy of all reported parameters for each evaluated test, and then a comparison of the parameters with the best DOR.

The image quality criteria are defined differently for each instrument and manufacturer and unfortunately they vary considerably among instruments and manufactures. The image quality algorithm of HRT is based on the mean pixel height standard deviation (MPHSD) in the mean topography image calculated from three consecutive single topographies. A value of MPHSD < 40 μ m is considered acceptable, <30 μ m is good and < 20 μ m very good. The GDx and different OCT instruments calculate,

according to different algorithms, a relative quality index (no unit provided) based on signal strength. All give a certain range and a recommended threshold for acceptable quality. The range and recommended thresholds (in brackets) for GDx&Cirrus OCT, Spectralis OCT, RTVue OCT and 3D OCT are 0-10 (≥ 6), 0-40 (≥ 15), 0-100 (≥ 40) and 0-100 (≥ 45), respectively.

3.2.1 Accuracy of OCT

Forty-seven studies (7,587 participants) assessed OCT. Twenty-three evaluated Cirrus, 18 RTVue, 10 Spectralis and one assessed 3D-2000 OCT. The median (range) sensitivity and specificity values reported were 74.8% (43.6-98%) and 86.7% (61.8-100%), respectively. In the nine studies in which the visual field test was used as reference standard, sensitivity ranged between 62.2% and 92.2%. The two studies defining glaucoma based on structural damage aimed at evaluating the capacity of OCT in detecting pre-perimetric glaucoma with localized RNFL defects. The parameter with highest sensitivity (67.6% - 88.5% in eyes with localized RNFL defects and normal perimetry) was average GCC. However, this figure was not significantly higher than that obtained by RNFL or ONH data.

Figure 3 describes a Forest plot of sensitivity and specificity of the individual studies, showing the heterogeneity of the sensitivities reported (Figure 3). Estimates of sensitivity, specificity and DOR were 0.78, 0.91 and 34.6; 0.79, 0.88 and 28.5; and 0.73, 0.85 and 15.4 for RNFL average thickness, average GCC thickness and average C/D ratio of OCT, respectively. Table 4 provides diagnostic accuracy estimates of the parameters evaluated. The hierarchical summary receiver operating characteristic curves for OCT parameters are presented in Figure 4. Comparing results between OCT parameters, RNFL and GCC variables were found to be significantly more accurate than tests considering average C/D ($p < 0.05$ after correction for multiple comparisons).

Image quality in OCT studies

Signal Intensity Score (SIS) values for OCT studies were as follows: 36 experimental units (EU) (66.6%) reported high signal strength images (cirrus > 7, Spectralis >30, RTVue >60, 3DOCT2000 >60), 9 EU used images with medium (cirrus 4.5-6.5, Spectralis 21-30, RTVue 46-60, 3DOCT2000 51-60) or high SIS requirements (16.6%), and in 9 EU OCT image quality criteria matched medium levels of SIS (16.6%). No studies included images with low levels of SIS (cirrus <4.5, Spectralis <21, RTVue <46, 3DOCT2000 <51).

3.2.2 Accuracy of HRT

Twenty-two studies, including 4,084 participants, investigated the HRT. Seventeen studies used HRT-3, 4 HRT-2 version 3.0 and only 1 employed HRT-1 images recalculated and converted into HRT-3 images. Across these 22 studies, the median (range) sensitivity and specificity values reported were 73.6% (30.6-95) and 82.7% (26-100) respectively. Using MRA criterion 1, sensitivity values ranged from 30.6% to 83% and specificity varied from 72% to 98%. With MRA criterion 2, sensitivity ranged from 57% to 93.7% and specificity varied from 55% to 100%. GPS algorithm evaluated at criterion 1 showed sensitivities ranging from 59% to 94.6% with specificities of 34.7% to 96.1%; and for GPS criterion 2 sensitivity was 58.2% to 93.9% and specificity ranged from 39.2% to 94.4%. Only seven of the studies included assessed rim area, finding high values of sensitivity (up to 95%) and specificity (up to 95%). Figure 5 includes a forest plot of each individual study. Table 5 shows the estimates of sensitivity, specificity and DOR of the parameters evaluated. Fifteen studies of 22 used as a reference standard visual field criteria while the remaining 7 chose both functional and structural measures as the reference standard.

MRA (criterion 2) was found significantly more sensitive, and MRA (criterion 1) was more specific ($p < 0.0001$ after correction for multiple comparisons). The diagnostic accuracy estimates for HRT parameters showed that MRA (criterion 2) and GPS (criterion 2) presented better sensitivity values, higher than 80%, while MRA (criterion 1) showed the highest specificity, higher than 90% (Table 5).

When considering overall test performance, MRA (criterion 2) presented the best results. Hierarchical summary ROC curves for the different parameters are presented in Figure 6.

Image quality in HRT studies

The quality criterion of the CSLO images was heterogeneous across studies. In 9 EU (37.5%) images including had poor ($>36\text{ }\mu\text{m}$) or medium (21 to $36\text{ }\mu\text{m}$) level standard deviation (SD) criteria, 2 EU (8.3%) included poor to high ($<20\text{ }\mu\text{m}$) SD criteria, 1 EU (4.1%) only used high quality images with low SD ($<20\text{ }\mu\text{m}$), 5 EU (25%) used medium level SD quality criteria, and 5 EU required medium or high ($<36\text{ }\mu\text{m}$) high SD quality criteria.

3.2.3 Accuracy of GDx

Twenty-two studies (3,618 participants) investigated GDx. A total of 5 EU reported diagnostic capacity with GDx-ECC and 20 with GDx-VCC. Two studies compared the two devices in the same sample of subjects. Across the studies, the median (range) sensitivity and specificity values reported for TSNIT and NFI were 75.9% (38.6-98) and 84.2% (45.3-100), respectively. Considering the different parameters evaluated, sensitivity, specificity and DOR were 0.80, 0.84 and 22.1 for Nerve Fiber Indicator (NFI); and 0.72, 0.86 and 15.8 for TSNIT Average, respectively. For GDx ECC, the sensitivities and specificities ranged from 72% to 96% and 80% to 95%, respectively. Table 6 shows sensitivity, specificity and DOR for GDx parameters. No significant statistical differences were found when comparing results between parameters. Figure 7 presents a forest plot of the sensitivity and specificity of the individual studies assessing GDx. Hierarchical summary ROC curves for GDx parameters are shown in Figure 8.

Image quality in GDx studies

The quality of the scans included in the studies was high (>8) in 17 EU (72%), medium (5-7) in 2 EU (8%) and medium or high in 5EU (20%). No studies included low quality images (< 5).

3.3 Comparison among imaging devices

When comparing the performance across the three instruments using the highest DOR, OCT presented the best results. Estimates of sensitivity, specificity and DOR were 0.78, 0.89 and 29.1 for OCT; 0.73, 0.84 and 13.9 for HRT and 0.77, 0.85 and 18.6 respectively for GDx. No statistically significant difference was found when comparing specificity, but sensitivity was significantly ($p < 0.05$) higher with OCT than with HRT or GDx (see Table 7). A comparison of the hierarchical summary ROC curves of each instrument is plotted in Figure 9.

3.4 Heterogeneity

To analyze heterogeneity in each of the devices separately, only two categories of DOR were used, defining low values as those under 18 and high values as those equal or over 18 (Table 8). Studies analyzing patients with early glaucoma ($MD < -5\text{dB}$ in visual field) showed low DOR (< 18) more frequently than those including patients with moderate level of disease. This tendency was statistically significant for OCT and GDx, but not for HRT. Ethnicity was also a significant factor of heterogeneity in OCT and GDx results, since studies including only white patients had high DORs (≥ 18) more frequently, while studies including Asian Indians or a mixed sample had low DORs more frequently.

3.5 Qualitative Analyses

This section will describe the main results of the screening studies selected. These studies assessed the devices as a tool for detecting glaucomatous optic nerve damage in a screening setting and in populations at risk for glaucoma. Six studies were included in this qualitative analysis. Four studies assessed the HRT, two GDx and one the OCT. The characteristics of each study are summarized in Tables 9 and 10. The data described as ranges of sensitivity and specificity reflect the results obtained for the same parameters investigated in the meta-analysis. In most studies the results found showed a lower

diagnostic accuracy of the instruments as screening devices when compared with their classification capabilities on preselected samples of the studies included in the meta-analysis. Many studies show low sensitivities or specificities clearly under 50%.

Only one screening study with OCT was included.(20) It reported sensitivity of 89% for average RNFL thickness. Using HRT, Kamdeu et al(21) (22) found that joining the categories probable glaucoma and glaucoma HRT obtained the lowest sensitivity value for MRA criterion 1 with 54.5% at 93.6% specificity, and the highest sensitivity for GPS criterion 2 with 85.7% at 64.3% specificity. Saito et al.(23) reported the diagnostic value for HRT based on the evaluation of 3021 Japanese subjects showing also the lowest sensitivity (29.6%) for MRA criterion 1 at specificity 96.1%, and the highest (85.2%) for GPS criterion 2 with 58.4% specificity, in a similar scenario grouping glaucoma together with glaucoma suspects. Finally, two screening studies (24) (25) used GDx and were performed by the same research group. They did not target a predefined population that could imply a low representation of population at high risk for glaucoma. GDx sensitivity values reported were low, ranging from 18.4% to 41%.

4. DISCUSSION

The use of imaging devices in glaucoma clinical practice has significantly increased during the last two decades. The images and data obtained from HRT, GDx and OCT have increased our knowledge about glaucoma and our competence to detect the disease, and could help to refine disease definition. At the same time it has also added a significant number of glaucoma suspects based on OCT results that could simply be false positive results. It is crucial to analyze fully the capabilities and limitations of such devices in order to incorporate them adequately into clinical practice. In this context we considered that a meta-analysis gathering a large amount of information reported in the last twenty years describing their diagnostic capabilities could be of great interest to clinicians and patients.

Summary of evidence

It has been suggested that a DOR of 25 could provide strong diagnostic evidence and that a DOR of 100 could provide convincing diagnostic evidence (26). In the present study the estimate of the summary DOR was 29.5 for OCT, 13.9 for HRT and 18.6 for GDx, confirming the presence of strong evidence about the clinical usefulness of OCT and, considerable but, slightly less optimal DOR values for GDx and HRT. This was not unexpected since developing companies stopped developing HRT and GDx ten to fifteen years ago and dedicated themselves fully to the improvement of OCT, a technology with great potential that has evolved enormously in the last 20 years. For all three instruments estimated sensitivity and specificity of best parameters was in the range of 80 to 90%. MRA was the best performing algorithm/parameter of HRT, with sensitivity of 0.80 and specificity of 0.85. NFI was the most sensitive (0.81) parameter of GDx with a specificity of 0.84. OCT sensitivity and specificity were 0.78 and 0.91 for RNFL thickness, 0.79 and 0.88 for GCC and 0.73 and 0.85 for C/D ratio, respectively. The parameters with the highest estimated specificities were RNFL and GCC for OCT, and MRA (criterion 1) for HRT, with values of 0.91, 0.88 and 0.91 respectively. Test accuracy, in particular sensitivity, was heterogeneous across studies, as is commonly found in this type of review study. Significant sources of heterogeneity were identified in degree of glaucomatous damage and ethnicity for OCT and GDx results.

Risk of bias assessment, performed with QUADAS-2, reported a high risk of bias in 49.3% of the studies in the patient selection domain, and related to the pre-selection of participants. Additionally, a high risk of bias was found in 25.9% of the studies in the flow and timing domain, associated with a time interval over 1 month between the index test and the reference standard, and the exclusion of some of the participants from the final analysis.

Limitations

Firstly, certain specific parameters from each device were chosen by the authors considering their clinical interest, clinical usage, and their presence in similar studies. Secondly, all studies included in the meta-analysis evaluated the ability to differentiate healthy subjects from confirmed glaucoma patients. This setting is in fact far from real clinical practice and could overestimate the diagnostic accuracy of HRT, GDx and OCT and for this reason some screening studies were also qualitatively analyzed (see results and comments below). Finally, although the electronic research process, inclusion criteria, QUADAS-2 items and data extraction forms were clearly defined and formalized in the study protocol, this process was performed by a single reviewer (MF) who consulted a second reviewer (AA) in doubtful cases.

Comparison with other reviews

Previous reviews on the diagnostic accuracy of imaging devices have been published. A recent Cochrane meta-analysis review used a very similar method and study design, with comparable results. (27) Of the 106 studies included, 40 assessed the GDx, 18 the HRT, and 63 the OCT. Michelessi et al (27) observed that the best parameters for diagnosing glaucoma were NFI for GDx (0.76 sensitivity, 0.92 specificity), average RFNL (0.72 sensitivity, 0.94 sensitivity) or inferior sector RNFL thickness for OCT and vertical C/D ratio or others for HRT (0.67 sensitivity and 0.94 specificity). One advantage of our study is that it included macular GCC parameters, commonly used nowadays, that were not included in Michelessi's meta-analysis. Nevertheless, the same research group formally compared GCC parameters to RNFL parameters (28) in patients with risk factors for glaucoma, in a different study using other methodology, and their results suggested that RNFL parameters are still preferable to macular parameters for diagnosing manifest glaucoma. Similarly, the present study showed DOR over the value of 25 for both RNFL (34.6) and macular GCC thickness (28.5), indicating that there is strong evidence of their capacity to classify normal and glaucomatous eyes, with slightly higher DOR value for the RNFL. These results could

possibly be biased by the fact that eyes with considerable para-papillary atrophy (myopia, oblique or tilted disks), in which macular GCC could be more reliable than peri-papillary RNFL measurements, are frequently excluded from this type of study. Other reviews assessing the role of OCT (29) (30) in glaucoma diagnosis found that RNFL was the most accurate parameter for the detection of glaucoma and that macular analyses show a comparable diagnostic capability. However, these two reviews did not include a methodological systematic evidence search, nor did they carry out a meta-analysis.

Regarding the heterogeneity results, Michelessi et al (27) restricted their analyses to the best parameters identified in the analysis. They found that sensitivity estimates were higher for studies with more severe glaucoma ($MD \geq 6$ dB). This finding was confirmed in our study. Additionally, the present study identified as a potential source of heterogeneity the ethnicity of subjects included in the sample. This is reasonable since databases do not include subjects of all ethnicities and very few instruments/versions offer the possibility of comparing each subject with a matching ethnicity-specific database.

Screening studies

Different studies have assessed the diagnostic accuracy of imaging devices in the context of screening in population at risk. This approximation is very useful and probably offers more realistic data. The present study included screening studies but could not perform a quantitative meta-analysis on them due to the heterogeneous methodology applied in those studies, so a qualitative analysis was carried out. A systematic comparative effectiveness review search with a specific focus on glaucoma screening was performed by Ervin et al (31) to June 2011. It included 17 studies on HRT-2, 11 on HRT-3, 47 studies on OCT and 27 on GDx. They reported sensitivity estimates of 0.68 (GPS) and 0.72 (MRA) at a fixed specificity of 92% for the best HRT3 parameters. Sensitivity and specificity estimates of OCT average RNFL thickness ranged from 0.24 to 0.96 and from 0.66 to 1.0, respectively. NFI sensitivity estimates

ranged from 0.28 to 0.99 at specificity levels between 0.53 and 0.95. Their results are comparable to our qualitative evaluation of the screening studies. In theory, the case-control study design could produce a valid estimate of test performance if the cases were sampled to match the reference standard positive patients (in terms of the spectrum of disease severity) and controls were matched to the reference standard negative patients (in terms of the spectrum of alternative conditions). In practice, however, this is very difficult to achieve (32). The qualitative contrast between the results of the meta-analysis and the results obtained in the context of screening provided more complete information on the detection capability of imaging devices. In screening studies, the setting, sample and results were more variable, heterogeneous and with lower diagnostic accuracy. This was an expected situation that confirmed the disadvantages of a case-control study design in the assessment of diagnostic tests.

In conclusion, this meta-analysis provides a systematic review of the capacity to classify normal subjects and glaucoma patients using OCT, HRT and GDx. All three instruments showed good diagnostic accuracy and OCT obtained best values of DORs. The best performing algorithm/parameters were MRA for HRT, NFI for GDx, and RNFL and GCC thickness for OCT. Further efforts should be made to assess the capabilities of imaging devices in the detection and follow-up of glaucoma patients, attempting to mimic the real-world clinical environment, so as to provide more powerful evidence to improve the management of glaucoma patients and suspects.

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Diagnostic Accuracy of Imaging Devices in Glaucoma: Meta-Analysis

TABLES

INSTRUMENT	PARAMETER
HRT3	Rim Area
	MRA Criterion 1 (normal+BL vs. ONL)
	Criterion 2 (normal vs. BL+ONL)
	GPS Criterion 1 (normal+BL vs. ONL)
GDX VCC-ECC	Criterion 2 (normal vs. BL+ONL)
	NFI
OCT(SD)	TSNIT Average
	Average RNFL
	Average GCC*
	C/D area ratio

Table 1. Variables extracted for each instrument (Index Test)

MRA (Moorfield Regression Analysis); ONL (Outside Normal Limits); BL (Borderline); GPS (Glaucoma Probability Score); NFI (Nerve Fiber Indicator); TSNIT (Temporal-Superior-Nasal-Inferior-Temporal); RNFL (Retinal Nerve Fiber Layer); GCC (Ganglion Cell Complex); C/D (Cup-To-Disc)

*Different studies measured the three innermost retinal layers, namely, the RNFL, the ganglion cell layer (RGC) and the inner plexiform layer (IPL) together (RNFL+RGC+IPL), others combined RGC + IPL and few measured only RGC layer. For the purpose of this study the term GCC was used interchangeably for all three combinations.

Diagnostic Accuracy of Imaging Devices in Glaucoma: Meta-Analysis - Tables and Figures

DOMAIN	key points
Patient Selection	<ul style="list-style-type: none"> • Adequate description of the population. • Case-control design was accepted as low risk, only if there were more than one control groups and diagnostic were still not confirmed. • Exclusions of patients with pathologies that may affect the realization of the test, don't were considered inadequate.
Index Test	<ul style="list-style-type: none"> • Clearly description of test performance (GDX, OCT, HRT) and well explained diagnostic criteria. • Performance of the index test in blind manner to the reference standard. • Reproducibility of the method in clinical practice
Reference Standard	<ul style="list-style-type: none"> • Clearly description of performance of reference standard and well explained diagnostic criteria. • Performance of the reference standard in blind manner to the index test. • Reproducibility of the method in clinical practice
Flow and Timing	<ul style="list-style-type: none"> • Lost cases and uninterpreted test properly explained. • Total number of patients and eyes analyzed. • Carrying time between the index test and the reference standard was considered optimal less than 1 month. • Execution of the index test and reference standard in all subjects of the sample.

Table 2. Key points for Quality Assessment of Diagnostic Accuracy Studies, version 2 (QUADAS-2) Evaluation.

Diagnostic Accuracy of Imaging Devices in Glaucoma: Meta-Analysis - Tables and Figures

Characteristics	Number	Number of studies
Participants enrolled	14853	81
Analyzed Eyes ¹	13778	81
Age: median (range) ₂	58.4±12.4 (38-71)	81
<i>Ethnic group (%)</i>		
White	5882	33 (40.7)
Asian	4153	26 (32)
Indian	1588	9 (11.1)
Mixed	1883	11 (13.5)
No Reported	272	2 (2.4)
<i>Test reported³ (number analyzed)</i>		
OCT	7204	54
HRT	4084	24
GDx	3618	25

Table 3. Summary of the characteristics of the studies included in the Meta-Analysis.¹Studies where the number of eyes does not indicate the number of subjects was considered.²Studies that do not report this data were not included in these calculations³Number of studies corresponds to experimental units statistically analyzed for each device

Diagnostic Accuracy of Imaging Devices in Glaucoma: Meta-Analysis - Tables and Figures

OCT Parameters	Sensitivity	Specificity	DOR	EU
RNFL	0.78 (0.74-0.83)	0.91 (0.88-0.93)	34.6 (21.6-47.7)	50
Average GCC	0.79 (0.71-0.88)	0.88 (0.82-0.94)	28.5 (10.7-46.3)	14
C/D area ratio	0.73 (0.63-0.84)	0.85 (0.80-0.90)	15.4 (7.1-23.6)	14

Table 4. Estimates of Sensitivity, Specificity and DOR for OCT parameters.

Values given at 95% confidence intervals. RNFL: Retinal Nerve Fiber Layer; GCC: Ganglion Cell Complex; C/D: Cup to disc Ratio; EU: Experimental Units.

HRT Parameters	Sensitivity	Specificity	DOR	EU
Rim Area	0.69 (0.46-0.86)	0.85 (0.68-0.99)	12.4 (3.4-21.3)	7
MRA (1)	0.66 (0.59-0.73)	0.91 (0.87-0.93)	18.7 (9.5-27.9)	17
MRA (2)	0.80 (0.75-0.85)	0.85 (0.77-0.93)	22.1 (8.8-35.4)	14
GPS (1)	0.74 (0.67-0.80)	0.80 (0.71-0.88)	10.9 (6.3-15.6)	14
GPS (2)	0.81 (0.73-0.88)	0.69 (0.55-0.83)	9.5 (5.3-13.6)	10

Table 5. Estimates of Sensitivity, Specificity and DOR for HRT parameters.

Values given at 95% confidence intervals. MRA (Moorfield Regression Analysis); GPS (Glaucoma Progression Score). Numbers (1) and (2) refer to more or less strict glaucoma definition criteria (see table 1 for variables definition)

Diagnostic Accuracy of Imaging Devices in Glaucoma: Meta-Analysis - Tables and Figures

GDx Parameters	Sensitivity	Specificity	DOR	EU
NFI	0.80 (0.74-0.87)	0.84 (0.81-0.88)	22.1 (10.8-33.4)	24
TSNIT	0.72 (0.65-0.78)	0.86 (0.81-0.91)	15.8 (8.6-22.9)	23

Table 6. Estimates of Sensitivity, Specificity and DOR for GDx parameters. Values given at 95% confidence intervals. NFI-Nerve Fiber Indicator
TSNIT- Temporal-Superior-Nasal-Inferior-Temporal Average

Device	Sensitivity	Specificity	DOR	EU
OCT	0.78 (0.74-0.82)	0.89 (0.87-0.92)	29.1 (19.8-38.5)	58
HRT	0.73 (0.70-0.76)	0.84 (0.79-0.88)	13.9 (9.4-18.5)	24
GDx	0.77 (0.71-0.83)	0.85 (0.81-0.89)	18.6 (10.8-26.5)	25

Table 7. Comparison of the diagnostic performance between instruments.

Diagnostic Accuracy of Imaging Devices in Glaucoma: Meta-Analysis - Tables and Figures

Variable		OCT			GDX			HRT		
		DOR low	DOR High	P value	DOR low	DOR High	P value	DOR low	DOR High	P value
RACE	White	27.8%	72.2%	<0.001	34.5%	65.5%	<0.001	73.5%	26.5%	0.263
	Asian	25%	75%		60%	40%		37.5%	62.5%	
	Hindu	66.7%	33.3%		100%	0%		55.6%	44.4%	
	Mixed race	91.7%	8.3%		100%	0%		66.7%	33.3%	
LEVEL OF GLAUCOMA	Early glaucoma ^a	67.9%	32.1%	<0.001	85.7%	14.3%	<0.001	76.5%	23.5%	0.123
DETECTED	Moderate glaucoma ^b	18.2%	81.2%		20.8%	79.2%		54.6%	45.4%	

Table 8. Heterogeneity results for each instrument.

DOR Low <18; DOR high ≥18

^aEarly glaucoma (MD -0.01 to -5.00 dB)^bModerate glaucoma (MD -5.01 to -12.00 dB)

Diagnostic Accuracy of Imaging Devices in Glaucoma: Meta-Analysis - Tables and Figures

Characteristics	Number	Number of studies
Participants enrolled	3651	6
Analyzed Eyes	3594	6
Age: median (range)	62.8±11.2	6
<i>Ethnic group (eyes analyzed)</i>		
White	701	4
Asian	2297	1
Mixed (Black , Caucasian)	221	1
Mixed (Black , Caucasian, Hispanic)	375	1
<i>Test reported (eyes analyzed)</i>		
OCT	138	1*
HRT	3111	4*
GDx	563	2*

Table 9. Summary characteristics of the studies included in the qualitative analysis

*experimental units

Study	Index Test	Reference Standar	Enrolled (n)	Analyzed (n)	Mean Age (range)	Sensitivity (%) (range)**	Specificity (%) (range)**	MD* (dB) (range)	Study period
Bengtsson 2012 Sweden	Cirrus OCT	OE VF GDx	307	138	68 (48-83)	89	95	4.58 (-15.8 - +0.07)	N/R
Kamdeu Fansi 2011 Canada	HRT3	OE VF	387	375	65±11	PssG and PG grouped with N (57.1 – 100) PG grouped with DG (43 – 89.9)	PssG and PG grouped with N (49.8 – 85) PG grouped with DG (53.4 – 89)	N/R	2003 - 2008
Kamdeu Fansi 2011 Canada	HRTII exported to HRT3 (Version 3.0)	OE VF	291	221	61±11	PssG and PG grouped with N (21.9 – 100) PG grouped with DG (32.7 – 96.2)	PssG and PG grouped with N (53.6 – 93.8) PG grouped with DG (57.1 – 96.4)	N/R	2003-2004
Saito 2009 Japan	HRT II version 3.0	OE VF color photo	3021	2297	59.4±10.4	G vs. N (28.5 – 93.7) G and GS vs. N (22 – 90.6)	G vs. N (56.4 – 96.8) G and GS vs. N (56.4 – 96.8)	-4.90±5.50	2000-2001
Tóth 2006 Hungary	GDxVCC	OE VF	233	181	61.5 ± 11.4 (16-83)	(18.4 – 41)	(87.6 – 97.7)	N/R	2006
Tóth 2008 Hungary	HRTII version 3.0 GDxVCC/ECC	OE VF	136	118	64.5 ± 9.9 (30-84)	GDx (23.8 – 39.1) HRT (42.9 – 85.7)	GDx (88.8 – 96.8) HRT (39.9 – 82)	N/R	2006

Table 10. Characteristics of screening programs included in qualitative analyses.

OE: Ophthalmic examination; VF: Visual Field; N: Normal; GS: Glaucoma Suspect; G: Glaucoma; PssG: Possible glaucoma; PG: Probably glaucoma; DG: Definite glaucoma.

*MD (median) reported for glaucoma subjects.

** Range the results corresponds at the same variables extracted for each instrument in the meta-analyses

Diagnostic Accuracy of Imaging Devices in Glaucoma: Meta-Analysis

FIGURE 1

Flowchart showing the distribution of the studies through the review process. *One study was performed with two different settings (screening population based-sample and selected glaucoma patients) and, for this reason, is counted in both categories and formed part of the qualitative and the quantitative evaluations.

OHT: Ocular Hypertension; GS: Glaucoma suspect.

Figure 2

Risk of Bias and Applicability concerns graph (QUADAS-2). Based on author's judgment about each domain evaluated following QUADAS-2 protocol. Risk of bias was classified as low, high or unclear. The distribution of the studies in the three categories is described as a percentage.

Appendix 1. Search Strategy of the systematic Review and Meta-Analysis.

Search descriptors and clues used for the electronic search from 1 January 1983 to 28 February 2015.

MEDLINE

#1 exp glaucoma, open angle AND diagnosis

#2 exp ocular hypertension AND diagnosis

#3 exp optic nerve diseases AND diagnosis

#4 OR 1-3

#5 glaucoma AND photography OR stereo photo^a

#6 glaucoma [MeSH terms] AND diagnosis [MeSH major topic] AND photography OR stereo photo^a

#7 glaucoma AND eye photography AND RNFL AND black and white photography^a

#8 (photographs or stereophotos\$.tw^a

#9 (black and white photographs\$.tw^a

#10 glaucoma AND scanning laser polarimetry

#11 glaucoma AND scanning laser polarimetry AND sensitivity

#12 retinal nerve fiber layer AND glaucoma

#13 SLP. tw

#14 GDx. tw

#15 VCC OR variable corneal compensant\$. Tw

#16 enhanced corneal compensant\$. Tw

#17 glaucoma AND Optical coherence tomography

#18 glaucoma AND Optical coherence tomography AND sensitivity

#19 glaucoma AND Confocal scanning laser ophthalmoscopy

#20 glaucoma AND confocal Scann\$ Laser Ophthalm\$ AND sensitivity

#21 (Heidelberg retina tomograph\$.tw

#22 HRT III.tw

#23 OR/ 5-24

#24 4 AND 23

COCHRANE LIBRARY

#1 glaucoma or POAG AND diagnosis in all fields

#2 ocular hypertension AND diagnosis in all fields

#3 optic nerve diseases AND diagnosis OR diagnostic techniques, ophthalmological in MeSh products

#4 #1 OR #2 OR #3

#5 glaucoma AND MeSH descriptor Photography

#6 glaucoma AND eye photography AND RNFL^a

#7 photograph* or stereophoto*.ti,ab AND Glaucoma

#8 black and white photograph\$ AND Glaucoma^a

#9 scan* laser polarimet* in All Fields AND Glaucoma

#10 scan\$ laser\$ polarimetry. ti,ab

#11 SLP AND Glaucoma

#12 GDx AND Glaucoma

#13 VCC AND Glaucoma

#14 ECC OR enhanced corneal compensant*

#15 Optical coherence tomogra*in All Fields AND Glaucoma

#16 MeSH descriptor Tomography, Optical coherence in all fields AND retina nerve fiber in all fields AND Glaucoma

#17 Optical coherence tomograph*.ti,ab

#18 OCT.ti,ab

#19 hrt III in All Fields OR confocal Scann* Laser Ophthalm* in All Fields AND GLAUCOMA

#20 Heidelberg retina tomograph*.ti,ab

#21 HRT III.ti,ab

#22 (#5 OR #6 OR #7 OR #8 OR #9 OR 10 OR #11 OR #12 OR #13 OR #14

OR #15 OR 16 OR #17 OR #18 OR #19 OR #20 OR #21)

#22 #4 AND #22

OPHTHALMOLOGY JOURNALS

(Journal of Glaucoma, Invest Ophthalmol Vis Sci, American Journal of Ophthalmology, British Journal of Ophthalmology)

Glaucoma AND diagnosis OR sensitivity OR specificity OR detect OR detected OR detection.

Glaucoma AND photography OR eye photography AND RNFL AND black and white photography^a

Glaucoma OR POAG (ti ab) AND Scanning laser polarimetry OR GDX VCC OR GDX ECC OR Optical coherence tomography OR OCT OR Confocal Scanning Laser Ophthalmoscope OR HRT.

Ophthalmology Journals referenced in EMBASE:

(Annals of Ophthalmology, Biomedical Optics Express, Case Reports in Ophthalmology, Global Advances in Health and Medicine, Health and Technology, Imagen Diagnostica, Imaging, International Eye Science, Journal of Ophthalmic Inflammation and Infection, Neuro-Ophthalmology, Neuro-Ophthalmology Japan, Retina-Vitreous, Revue Francophone d'Orthoptie)

Glaucoma AND diagnosis OR sensitivity OR specificity OR detect OR detected OR detection.

Glaucoma AND photography OR eye photography AND RNFL AND black and white photography^a

Glaucoma OR POAG (ti ab) AND Scanning laser polarimetry OR GDX VCC OR GDX ECC OR Optical coherence tomography OR OCT OR Confocal Scanning Laser Ophthalmoscope OR HRT.

^a The Search strategy also includes Retinography and Red free photos.
The results generated by these descriptors will be published separately.

Appendix 2.

The following is a list of excluded studies in order of cause of exclusion. They are shown in alphabetical order.

2.a Outcomes required not reported (n=36)

Baskaran M, Ong Ee-Lin, Li Jia-Liang, Cheung C, Chen D, Perera S A, Ho Ching Lin, Zheng Ying-Feng, Aung Tin; Classification algorithms enhance the discrimination of glaucoma from normal eyes using high-definition optical coherence tomography. *Investigative Ophthalmology & Visual Science* April 2012, Vol.53, 2314-2320.

Chen Hsin-Yi, Chang Yue-Cune, Wang I-Jong, Chen Wen-Chi; Comparison of glaucoma diagnoses using Stratus and Cirrus optical coherence tomography in different glaucoma types in a Chinese population. *J Glaucoma*. 2013 Oct-Nov;22(8):638-46.

Chen Junyi, Huang Haili, Wang Min, Sun Xinghuai, Qian Shaohong; Fourier domain OCT measurement of macular, macular ganglion cell complex, and peripapillary RNFL thickness in glaucomatous Chinese eyes. *Eur J Ophthalmol*. 2012 Nov-Dec;22(6):972-9.

Correnti Anthony J, Wollstein Gadi, Price Lori Lyn, Schuman Joel S; Comparison of optic nerve head assessment with a digital stereoscopic camera (discam), scanning laser ophthalmoscopy, and stereophotography. *Ophthalmology*. 2003 Aug;110(8):1499-505.

Elbendary Amal M, Mohamed Helal Randa; Discriminating ability of spectral domain optical coherence tomography in different stages of glaucoma. *Saudi J Ophthalmol*. 2013 Jan;27(1):19-24.

Firat Penpe Gul, Doganay Selim, Demirel Ersan Ersin, Colak Cemil; Comparison of ganglion cell and retinal nerve fiber layer thickness in primary open-angle glaucoma and normal tension glaucoma with spectral-domain OCT. *Graefes Arch Clin Exp Ophthalmol*. 2013 Mar;251(3):831-8.

Guvant Pinakin, Zheng Yufeng, Tóth Marta, Holló Gábor. Atypical retardation pattern: can performance of classification be improved?. *Optom Vis Sci*. 2008 Jun;85(6):482-8.

Hae Young L Park, Chan Kee Park; Structure-function relationship and diagnostic value of RNFL Area Index compared with circumpapillary RNFL thickness by spectral-domain OCT. *J Glaucoma*. 2013 Feb;22(2):88-97.

Hoesl Laura M, Mardin Christian Y, Horn Folkert K, Juenemann Anselm G M, Laemmer Robert; Influence of glaucomatous damage and optic disc size on glaucoma detection by scanning laser tomography. *J Glaucoma*. 2009 Jun-Jul;18(5):385-9.

Holló G, Naghizadeh F, Vargha ; Accuracy of Macular Ganglion-Cell Complex Thickness to Total Retina Thickness Ratio to Detect Glaucoma in White Europeans. *J Glaucoma*. 2014 Oct-Nov;23(8):e132-7.

Hong, Samin , Seong Gong Je, Kim Sung Soo, Kang Sung Yong, Kim Chan Yun; Comparison of peripapillary retinal nerve fiber layer thickness measured by spectral vs. time domain optical coherence tomography. *Curr Eye Res*. 2011 Feb;36(2):125-34.

Huang, Lina, Fan Ning, Shen Xiaoli, He Jing; Comparison of the diagnostic ability of retinal nerve fiber layer thickness measured using time domain and spectral domain optical coherence tomography in primary open angle glaucoma. *Eye Sci*. 2011 Sep;26(3):132-7, 142.

Huang Mei-Ling , Chen Hsin-Yi, Huang Wei-Cheng, Tsai Yi-Yu; Linear discriminant analysis and artificial neural network for glaucoma diagnosis using scanning laser polarimetry-variable cornea compensation measurements in Taiwan Chinese population. *Graefes Arch Clin Exp Ophthalmol*. 2010 Mar;248(3):435-41.

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ID study	Type study	Test	Reference standar	Study period (months)	Mean Age (years)	Recruitment	Ethnicity	Number of subjects enrolled	Number of subjects analized	Level of glaucoma patients *
Akashi Azusa 2013 Japan	Case-Control Cross-Sectional	Cirrus OCT RTvue OCT 3D OCT 2000 Quality Image: good	Functional Structural	N/R	45.55±11.1	Defined by criteria	Asian	232	N/R	Moderate
Barella Kleyton Arlindo 2013 Brazil	Observational Cross-Sectional	Cirrus OCT Quality Image: Medium-good	Functional	N/R	58.2±8.95	Defined by criteria	Mixed	110	103	Early
Bengtsson Boel 2012 Sweden	Observational Cross-Sectional (Retrospective Selection)	Cirrus OCT Quality Image: Good	Funcional Structural	N/R	71	Defined by criteria	N/R	164	138	Early to Advanced
Benitez Del Castillo Javier 2011 Spain	Crossover Observational Study	GDxVCC GDxECC Cirrus OCT Quality Image: good	Funcional Structural	N/R	61.45±10.4	Consecutive, Defined by criteria	Caucasian	117	88	Moderate
Bertuzzi Francesca 2013 Italy	Observational Cross-Sectional	RTVue OCT GDx ECC Quality Image: medium- good good (resp.)	Functional	12	61.42±11.69	Defined by criteria	Caucasian	205 (70 Glaucoma, 65 OHT, 70 Normal)	205	Moderate
Borque E 2008 Spain	Case-Control Cross-Sectional	GDxVCC Quality Image: good	Functional Structural	12	59.36±10.55	Consecutive, Defined by criteria	Caucasian	417 (139 POAG, 218 OHT, 60 N)	199	Early -Moderate
Bozkurt Banu 2010 Turkey	Case-Control Cross-Sectional	HRT3 Quality Image: medium	Functional Structural	N/R	61.3±10.2	Defined by criteria	Caucasian	342	342	Moderate
Brusini Paolo 2006 Italy	Observational Case-Control Cross-Sectional	GDxVCC Quality Image: good	Functional	3	68.5±9.95	Defined by criteria	Caucasian	157	157	Early

ID study	Type study	Test	Reference standar	Study period (months)	Mean Age (years)	Recruitment	Ethnicity	Number of subjects enrolled	Number of subjects analized	Level of glaucoma patients *
Calvo Pilar 2014 Spain	Case-Control Cross-Sectional	HRT3 Quality Image: medium	Functional	1	60.3	Consecutive, Defined by criteria	Caucasian	350	338	Moderate
Chen Hsin-Yi 2008 China	Case-Control Cross-Sectional	GdxVCC Quality Image: good	Functional Structural	12	60.46±9.1	Defined by criteria	Asian	133 (47 HTPOAG, 41 PACG, 45 N)	133	Early
Chen Hsin-Yi 2007 China	Case-Control Cross-Sectional	GDxVCC Quality Image: good	Functional Structural	N/R	45.81±14.62	Defined by criteria	Asian	189 (82 POAG, 45 GS, 62N)	189	Early
Cho Jung Woo 2011 Korea	Case-Control Cross-Sectional	Spectral OCT Quality Image: good	Functional Structural	7	49.2±15.25	Consecutive, Defined by criteria	Asian	92	92	Moderate
Choi Yun Jeong 2013 Korea	Observational Cross-Sectional	Spectral OCT Quality Image: medium-good	Functional Structural	7	48.43±13.11	Consecutive, Defined by criteria	Asian	207 (49 highly myopic, 54 nonhighly myopic POAG, 78N)	181	Moderate
Coops Annemiek 2006 United Kingdom	Case-Control Cross-Sectional And Cohort Longitudinal	HRTI recalculated and converted in HRT3 Quality Image: poor-medium-good	Functional	72	64.95	Consecutive, Defined by criteria	Caucasian	216	205	Early
Da Pozzo Stefano 2006 Italy	Case-Control Cross-Sectional	GDxVCC Quality Image: good	Functional Structural	10	65.75±7.65	Defined by criteria	Caucasian	124	110	Early
Da Pozzo Stefano 2005 Italy	Observational Case-Control Cross-Sectional	GDxVCC Quality Image: good	Functional Structural	7	65.85±8.3	Defined by criteria	Caucasian	124	124	Moderate

ID study	Type study	Test	Reference standar	Study period (months)	Mean Age (years)	Recruitment	Ethnicity	Number of subjects enrolled	Number of subjects analyzed	Level of glaucoma patients *
DeLeón-Ortega Julio E. 2006 USA	Case-Control Cross-Sectional (Retrospective Selection)	GDxVCC Quality Image: medium	Functional Structural	2	48.15±12.6	Defined by criteria	Mixed	228	228	Early
DeLeo'n-Ortega Julio E. 2007 USA	Case-Control Cross-Sectional (Retrospective Selection)	HRT II version 3.0 Quality Image: good	Functional Structural	2	48.42±8.82	Defined by criteria	Mixed	167	167	Early
Ferreras Antonio 2007 Spain	Observational Cross-Sectional	HRT3 Quality Image: poor-medium	Functional Structural	6	60.65±8.58	Consecutive, Defined by criteria	Caucasian	201	186	Moderate
Ferreras Antonio 2009 Spain	Case-Control Cross-Sectional	GDxVCC Quality Image: good	Functional Structural		59.68±8.39	Defined by criteria	Caucasian	148 (validating set)	144	Moderate
Florent Aptel 2010 France	Case-Control Cross-Sectional	GDxVCC Cirrus OCT Quality Image: good	Functional Structural	N/R	62±12.33	Defined by criteria	Caucasian	166 (40POAG, 40GS, 40N)	120	Moderate
Garas A. 2011 Hungary	Observational Cross-Sectional	RTVue OCT Quality Image: medium	Functional Structural	11	56.55±14.72	Defined by criteria	Caucasian	286 (157 POAG, 36 OHT, 93N)	286	Early -Moderate
Garudadri Chandra S. 2012 India	Case-Control Cross-Sectional	GDxVCC Quality Image: good	Functional Structural	21	53.92±10.20	Defined by criteria	Indian	220	220	Moderate
Harizman N 2006 USA	Case-Control Cross-Sectional	HRT3 Quality Image: Poor-medium	Functional Structural	N/R	52±12.7	Defined by criteria	Mixed	220	217	Moderate
Hong Samin 2007 Korea	Case-Control Cross-Sectional	GDxVCC Quality Image: medium	Functional Structural	1	38.25±14.6	Defined by criteria	Asian	120	120	Early

ID study	Type study	Test	Reference standar	Study period (months)	Mean Age (years)	Recruitment	Ethnicity	Number of subjects enrolled	Number of subjects analized	Level of glaucoma patients *
Ieite Mauro T. 2011 USA	Case-Control Cross-Sectional	Cirrus OCT Spectral OCT RTvue OCT Quality Image: medium- good good medium- good (resp.)	Functional	N/R	60±14.5	Defined by criteria	Mixed	149	233	Moderate
Jeoung Jin Wook 2013 Korea	Case-Control Cross-Sectional	Spectral OCT Quality Image: good	Functional Structural	12	55.9±11.2	Consecutive, Defined by criteria	Asian	107	107	Early
Jeoung Jin Wook 2013 Korea	Case-Control Cross-Sectional	Cirrus OCT Quality Image: good	Functional Structural	1	58.33±11.86	Defined by criteria	Asian	545	425	Early Moderate to Severe
Jeoung Jin Wook 2010 Korea	Case-Control Cross-Sectional	Cirrus OCT Quality Image: medium- good	Functional Structural	6	53.75±10.5	Consecutive, Defined by criteria	Asian	170	151	Normal
Jindal Shveta 2010 India	Case-Control Cross-Sectional	HRT3 Quality Image: medium	Functional Structural	N/R	51.79±9.98	Defined by criteria	Indian	100	100	Moderate
Kiddee Weerawat 2013 Thailand	Case-Control Cross-Sectional	Cirrus OCT Quality Image: good	Functional Structural	8	N/R	Defined by criteria	Asian	131 (48 POAG, 48 GS, 35 N)	131	Early, Moderate, Severe.
Kim Ko Eun 2013 Japan	Case-Control Cross-Sectional	Cirrus OCT Quality Image: good	Functional Structural	36	60.85±11.4	Defined by criteria	Asian	346	248	Moderate
Kim Mi Jeung 2014 Korea	Case-Control Cross-Sectional	Cirrus OCT Quality Image: good	Functional Structural	N/R	57.7±11.35	Defined by criteria	Asian	209	184	Normal

ID study	Type study	Test	Reference standar	Study period (months)	Mean Age (years)	Recruitment	Ethnicity	Number of subjects enrolled	Number of subjects analized	Level of glaucoma patients *
Kim Na Rae 2013 Korea	Case-Control Cross-Sectional	RTVue OCT Quality Image: good	Functional Structural	6	56.11±13.74	Consecutive, Defined by criteria	Asian	161 (52 POAG, 51 NTG, 58 N)	161	Moderate
Kita Yoshiyuki 2013 Japon	Case-Control Cross-Sectional	RTVue OCT Quality Image: good	Functional Structural	18	53.86±11.2	Defined by criteria	Asian	134	134	Early -Moderate
Kyung Min Koh 2014 Korea	Case-Control Cross-Sectional (Control Group Ongoing Poblacional Study)	Cirrus OCT Spectral OCT Quality Image: medium good (resp.)	Functional Structural	6	59.6±14.4	Consecutive, Defined by criteria	Asian	110	110	Moderate
Kratz Assaf 2014 Australia	Observational Cross-Sectional	HRT3 Quality Image: medium	Functional	12	68.6±6.55	Defined by criteria	N/R	173	173	Moderate
Lee Suhwan 2010 Korea	Case-Control Cross-Sectional	Cirrus OCT GDxVCC Quality Image: good	Functional Structural	12	55.4±11.1	Defined by criteria	Asian	165	165	Moderate
Leung Kai- shun Christopher 2010 China	Observational Case-Control Cross-Sectional	HRT3 Spectral OCT Quality Image: medium- good good (resp.)	Functional	5	50.66±13.99	Defined by criteria	Asian	155	155	Moderate
Lester Michele 2008 Italy	Case-Control Cross-Sectional	HRT3 Quality Image: Poor - medium	Functional	N/R	65.9±12.1	Consecutive, Defined by criteria	Caucasian	214	214	Early
Mai T. A. 2007 Holland	Observational Cross-Sectional	GDxVCC GDxECC Quality Image: Medium-good	Functional Structural	N/R	63.3±11.45	Defined by criteria	Caucasian	133	133	Moderate

ID study	Type study	Test	Reference standar	Study period (months)	Mean Age (years)	Recruitment	Ethnicity	Number of subjects enrolled	Number of subjects analyzed	Level of glaucoma patients *
Mansoori Tarannum 2011 India	Case-Control Cross-Sectional	Spectral OCT Quality Image: good	Functional Structural	N/R	57±8.55	Defined by criteria	Indian	178	178	Early
Mayama Chihiro 2014 Japan	Observational Cross-Sectional (Multicenter)	HRTII version 3.0 Quality Image: Medium-good	Functional Structural	24	50.25±8.27	Consecutive, Defined by criteria	Asian	254	254	Early to Moderate
Medeiros Felipe A. 2004 USA	Observational Cross-Sectional (Retrospective Selection)	GDxVCC Quality Image: Medium-good	Functional	N/R	66.05±11	Defined by criteria	Caucasian	114 (42 POAG, 32 GS, 40 N)	82	Moderate
Min Hee Suh 2013 Korea	Case-Control Cross-Sectional	Cirrus OCT Quality Image: good	Functional	15	56.45±11.3	Consecutive, Defined by criteria	Asian	172	158	Early
Moreno Pilar A.M. 2011 Brazil	Case-Control Cross-Sectional	RTVue OCT Quality Image: good	Functional Structural	N/R	60.4± 12.35	Consecutive, Defined by criteria	Mixed	123	123	Early
Moreno-Montañes Javier 2010 Spain	Case-Control Cross-Sectional	Cirrus OCT Quality Image: Medium	Functional	N/R	59.57 ±18.43	Defined by criteria	Caucasian	216 (first 30 Cirrus OCT were learning curve)	166	Early to advanced.
Moreno-Montañes Javier 2008 Spain	Observational Cross-Sectional	HRT3 Quality Image: Poor – medium	Functional	N/R	62.5	Consecutive, Defined by criteria	Caucasian	186 (83 POAG, 40 OHT, 59 N)	182	Early
Mwanza Jean-Claude 2014 USA	Case-Control Cross-Sectional (Multicenter)	Cirrus OCT Quality Image: Medium-good	Functional Structural	N/R	64.75±9.95	Defined by criteria	N/R	99	99	Early

ID study	Type study	Test	Reference standar	Study period (months)	Mean Age (years)	Recruitment	Ethnicity	Number of subjects enrolled	Number of subjects analyzed	Level of glaucoma patients *
Mwanza Jean-Claude 2011 USA	Case-Control Cross-Sectional	Cirrus OCT Quality Image: Medium	Functional Structural	N/R	59.65 ±11.1	Defined by criteria	Caucasian	219	219	Moderate
Na Jung Hwa 2013 Korea	Case-Control Cross-Sectional	RTVue OCT Quality Image: good	Structural	8	51.75±11.65	Consecutive, Defined by criteria	Asian	179	173	Early
Nouri-Mahdavi Kourus 2013 USA	Case-Control Cross-Sectional	Cirrus OCT Quality Image: good	Functional	23	62.35±7.6	Consecutive willing to participate in a tertiary setting.	Mixed	99	150	Early
Oddone Francesco 2008 Italy	Observational Cross-Sectional (Multicenter)	HRT3 Quality Image: Medium-good	Functional	N/R	61.8±12	Defined by criteria	Caucasian	242	238	Early, Moderate, Severe.
Oddone Francesco 2011 Italy	Observational Cross-Sectional	GDxVCC Cirrus OCT HRT3 Quality Image: good good Medium-good (resp.).	Functional	N/R	65.25±7.3	Consecutive, Defined by criteria	Caucasian	130	120	Moderate
Pablo Luis E. 2010 Spain	Case-Control Cross-Sectional	HRT3 Quality Image: Poor – medium	Functional	6	60.47±8.21	Defined by criteria	Caucasian	105	105	Early
Parikh Rajul S. 2008 India	Observational Cross-Sectional	GDxVCC Quality Image: good	Functional Structural	20	53.55±9.85	Consecutive, Defined by criteria	Indian	188	178	Early

ID study	Type study	Test	Reference standar	Study period (months)	Mean Age (years)	Recruitment	Ethnicity	Number of subjects enrolled	Number of subjects analized	Level of glaucoma patients *
Rao Harsha L. 2013 India	Case-Control Cross-Sectional	RTVue OCT Quality Image: good	Structural	36	52	Defined by criteria	Indian	166 (34 POAG, 72 N large optic disc cupping, 60 N)	94	Early
Rao Harsha L. 2010 India	Case-Control Cross-Sectional	HRT3 Quality Image: Poor-medium	Functional Structural	20	53.55±9.85	Defined by criteria	Indian	187	177	Moderate
Rao Harsha L. 2012 India	Case-Control Cross-Sectional	RTVue OCT Quality Image: good	Functional Structural	N/R	49.73±13.56	Defined by criteria	Indian	147 (46 POAG, 41GS, 60 N)	260	Early
Rao Harsha L. 2012 India	Observational Cross-Sectional	RTVue OCT Quality Image: good	Functional Structural	10	49.75±13.4	Consecutive, Defined by criteria	Indian	123	216	Early
Rao Harsha L. 2010 USA	Case-Control (As A Part Longitudinal Study Digs)	RTVue OCT Quality Image: good	Functional	N/R	65.34±11.29	Defined by criteria	Mixed	153	214	Early
Rao Harsha L. 2014 India	Observational Cross-Sectional	GDxECC RTVue OCT Quality Image: good Medium (resp.)	Functional Structural	26	53.5	Consecutive, Defined by criteria	Indian	255	165	Moderate
Robert T. Chang 2009 USA	Case-Control Cross-Sectional	Cirrus OCT Quality Image: good	Functional Structural	12	65.25±12.05	Defined by criteria	Caucasian	104	104	Early to Moderate

ID study	Type study	Test	Reference standar	Study period (months)	Mean Age (years)	Recruitment	Ethnicity	Number of subjects enrolled	Number of subjects analized	Level of glaucoma patients *
Roberti Gloria 2014 Italy	Observational Cross-Sectional	RTVue OCT HRT3 Quality Image: Medium-good (resp.)	Functional Structural	N/R	59.75±12.1	Defined by criteria	Caucasian	104	104	Moderate
Rolle Teresa 2011 Italy	Observational Cohort Study	RTVue OCT Quality Image: good	Functional Structural	12	57.95±6.81	Defined by criteria	Caucasian	178	178	Early
Sahin Sevim Mehmet 2013 Turkey	Case-Control Cross-Sectional	RTVue OCT Quality Image: Medium	Functional Structural	65	63.86±19.45	Consecutive, Defined by criteria	Caucasian	143	208	Early to Severe
Saito Hitomi 2009 Japan	Case-Control Cross-Sectional	HRT II version 3.0 Quality Image: Poor to good	Functional Structural	8	57.85±9.5	Defined by criteria	Asian	148	148	Early
Sánchez-Cano Ana 2009 USA	Observational Cross-Sectional	GDxVCC Quality image: Medium-good	Functional Structural	N/R	42.85±13.25	Consecutive, Defined by criteria	Caucasian	451	451	N/R
Sehi Mitra 2009 USA	Observational Cohort Study	RTVue OCT Quality Image: Medium	Functional Structural	N/R	66.5±10.2	Defined by criteria	Caucasian	110	100	Moderate
Seong Bae Park 2009 Korea	Case-Control Cross-Sectional	Cirrus OCT Quality Image: good	Functional Structural	9	52.5±11.3	Consecutive, Defined by criteria	Asian	174	174	Moderate
Shin Hyun Jin 2011 Korea	Case-Control Cross-Sectional	Spectral OCT Quality Image: good	Functional Structural	6	49.92±10.75	Defined by criteria	Asian	217 (26 POAG, 76 NTG, 91 GS, 24N)	126	Moderate

ID study	Type study	Test	Reference standar	Study period (months)	Mean Age (years)	Recruitment	Ethnicity	Number of subjects enrolled	Number of subjects analized	Level of glaucoma patients *
Sung Kyung Rim 2009 Korea	Case-Control Cross-Sectional	Cirrus OCT Quality Image: good	Functional Structural	6	52.76±11.6	Consecutive	Asian	163 (55 POAG, 48 GS, 60 N)	115	Moderate
Takmaz Tamer 2009 Turkey	Case-Control Cross-Sectional	HRT3 Quality Image: Medium	Functional Structural	N/R	58.55±10.5	Defined by criteria	Caucasian	160	160	Moderate
Takuhei Shoji 2010 Japan	Case-Control Cross-Sectional	Spectral OCT Quality Image: Medium	Functional Structural	24	54.55±12.9	Defined by criteria	Asian	90 (N and POAG with high myopia)	82	Moderate
Vessani Roberto M. 2009 Brazil	Case-Control Cross-Sectional	GDxECC HRT3 Quality Image: Medium-good Poor-medium (resp.)	Functional	2	62.2±9.85	Consecutive, Defined by criteria	Mixed	160	118	Early to advanced
Vidotti Vanessa 2013 Brazil	Observational Cross-Sectional	Cirrus OCT Quality Image: good	Functional Structural	27	65.45± 9.1	Defined by criteria	Mixed	110	110	Early
Wu Huijuan 2012 USA	Case-Control Cross-Sectional	Spectral OCT Quality Image: Poor	Functional Structural	12	66.4 ± 13.8	Defined by criteria	Caucasian	146	146	Moderate
Yuan Fang 2010 China	Observational Cross-Sectional	RTVue OCT Quality Image: good	Functional Structural	9	57.35±12.35	Defined by criteria	Asian	76	76	Early
Zangwill Linda M. 2007 USA	Case-Control Cross-Sectional From Cohort Longitudinal (Digs)	HRT II version 3.0 Quality Image: Poor to good	Functional	N/R	62.8	Defined by criteria	Caucasian	161	161	Moderate

ID study	Type study	Test	Reference standar	Study period (months)	Mean Age (years)	Recruitment	Ethnicity	Number of subjects enrolled	Number of subjects analized	Level of glaucoma patients *
Zeilefsky Joseph R. 2006 USA	Case-Control Cross-Sectional	HRT3 Quality Image: Poor-medium	Functional	N/R	50±14	Defined by criteria	Caucasian Black	220	220	Moderate
Zeppieri Marco 2010 Italy	Observational Case-Control Cross-Sectional (Multicenter)	GDxVCC Quality Image: good	Functional Structural	4	61.7±10.95	Defined by criteria	Caucasian	319 (75 POAG, 67 GON, 87 OHT, 90 N)	165	Early

* Level of disease severity reported. Based on the visual field (Bascom Palmer Hodapp-Parrish-Anderson) ²⁴⁻²⁸ Data obtained from the mean deviation (MD) dB reported in the study.

Functional: Evidence of reproducible visual field loss was considered glaucoma. Structural: Classification into glaucoma and nonglaucoma based on the presence or absence of characteristic glaucomatous optic disc changes.

POAG: Primary open angle glaucoma; HTPOAG: High tension Primary open angle glaucoma, PACG: Primary Angle closure glaucoma; GON: Glaucomatous Optic Nerve; N: Normal; DIGS: Diagnostic Innovations in Glaucoma Study; (resp.): respectively; N/R: Not reported.