Diagnostic Ability of Heidelberg Retina Tomography in Detecting Glaucoma in a Population Setting

The Singapore Malay Eye Study

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Objective: To evaluate the performance of the Heidelberg Retina Tomograph II (HRT II, Heidelberg Engineering, Heidelberg, Germany) in diagnosing glaucoma in a population setting.

Design: Population-based cross-sectional study.

Participants: Of 3280 Malay persons aged 40 to 80 years who participated in the survey, 112 subjects (124 eyes) with glaucoma and a subset of 196 bilaterally normal subjects (392 eyes) were included for the evaluation of diagnostic ability of HRT II.

Methods: All glaucomatous and normal eyes underwent standardized ophthalmic assessment (including automated perimetry) and HRT II. Glaucoma was defined according to International Society for Geographical and Epidemiological Ophthalmology criteria. Area under the curve (AUC) receiver operating characteristic (ROC), sensitivity, and specificity were used to evaluate the diagnostic performance of HRT II algorithms. Marginal logistic regression models were used to evaluate the influence of optic disc size on the results of HRT II algorithms.

Main Outcome Measures: The HRT II algorithms: linear discriminant functions (LDFs) by Mikelberg et al (LDF1), Burk et al (LDF2), Bathija et al (LDF3), and Moorfields regression analysis (MRA). The MRA was subdivided into MRA1 with "borderline" outcomes as positive and MRA2 with "borderline" outcomes as negative.

Results: Subjects with cataract, visual impairment, astigmatism, and greater negative spherical equivalent, and of older age were more likely to yield lower quality images. For analyses by eye, AUCs were 0.789, 0.704, 0.755, 0.754, and 0.762 for MRA1, MRA2, LDF1, LDF2, and LDF3, respectively. At 85% specificity, sensitivities were 62.1%, 65.3%, and 66.9% for LDF1, LDF2, and LDF3, respectively. At 95% specificity, these figures decreased to 31.5%, 42.7%, and 45.2%, respectively. The sensitivity and specificity were 71.0% and 86.7% for MRA1 and 43.6% and 97.2% for MRA2, respectively. Similar estimates were found for analyses by person. Larger optic disc size was associated with increased sensitivity and false-positive rate for MRA1, LDF1, and LDF2. LDF1 and LDF3 were least affected by optic disc area, but the sensitivities were moderate and the false-positive rates were high across different optic disc areas.

Conclusions: The current HRT II algorithms are of limited value for population-based glaucoma screening in the Malay population and do not account adequately for optic disc size.

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Glaucoma is currently the second leading cause of blindness worldwide, and it has been estimated that 60.5 million people will have this condition by 2010.[1] Most population-based studies have shown that more than half of the cases with glaucoma are undiagnosed.[2–4] This underscores the need for case-finding and glaucoma screening approaches in the community.[5,6] Such a strategy is critical because early treatment to lower intraocular pressure (IOP) could reduce the progression of visual field damage.[7]

The effectiveness of a population-based screening program requires that potential instruments and tests demonstrate acceptable sensitivity and specificity. A number of tests have been suggested for this purpose, but none have been demonstrated as optimal screening tools for glaucoma.[8] For example, clinical ophthalmoscopy of optic discs relies heavily on the examiner's skill and is subjective.[9] Measurement of visual fields is difficult because patient training, repeated tests, and reproducible results are required to confirm abnormality.[10] Measurement of IOP is limited by its overlapping distribution in normal and glaucomatous eyes.[11]

The Heidelberg Retina Tomograph II (HRT II, Heidelberg Engineering, Heidelberg, Germany) is a scanning laser ophthalmoscope that uses a diode laser (670 nm

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wavelength) to sequentially scan the retinal surface, and a 3-dimensional topographic image is constructed from a series of sectional images at consecutive focal planes. The instrument provides reproducible and real-time scans of the optic disc and retinal nerve fiber layer. The potential use of HRT II as a single screening tool for glaucoma has been suggested by several studies.[12–14] However, none of these studies were conducted in a randomly selected general population sample, with the exception of the Bridlington Eye Assessment Project (BEAP), which included a randomly selected population aged more than 65 years. This study assessed the accuracy of the HRT II to diagnose glaucoma in a population-based study of Asian Malays aged 40 to 80 years in Singapore.

Subjects and Methods

Population Sampling

The Singapore Malay Eye Study (SiMES) examined 3280 persons (78.7% response) of Malay ethnicity aged 40 to 80 years between August 2004 and June 2006.[4,15] The methods for this survey and recruitment process have been described in detail.[16] Ethics approval was obtained from the institutional review board of the Singapore Eye Research Institute, Singapore, and the study was conducted in accordance with the World Medical Association's Declaration of Helsinki. Informed written consent was obtained from all participants.

Ophthalmic Examination

Before the study, the study ophthalmologists were trained in the Van Herick technique, gonioscopy, and the assessment of optic disc characteristics.[4] A comprehensive interview and ocular examination were carried out in the Singapore Eye Research Institute for all participants.[4] A slit-lamp (model BQ-900, Haag-Streit, Bern, Switzerland) examination was performed for the anterior segment, and the Van Herick technique was used to estimate temporal peripheral anterior chamber depth.[17] Intraocular pressure was measured using a Goldmann applanation tonometer (Haag-Streit, Bern, Switzerland) before pupil dilation. Gonioscopy was performed with a Goldmann-type 2-mirror gonioscope on 3 groups of participants: (1) those with suspected glaucoma (see below for definition), (2) all participants with a shallow peripheral anterior chamber (Van Herick $\leq$ grade 2), and (3) 1 in 5 randomly selected participants not meeting the first 2 criteria.[4]

After pupil dilation, the optic disc was evaluated using a +78 diopter (D) lens at $\times$16 magnification with a measuring graticule (Haag-Streit). The margins of the optic cup were defined stereoscopically as the point of maximal inflection of vessels crossing the neuroretinal rim. The vertical cup diameter was measured as the vertical distance between the points of maximal centrifugal extension of the cup between 11 and 1 o'clock and 5 and 7 o'clock. The vertical cup-to-disc ratio (VCDR) was then calculated. For small optic discs with no visible cup, the measurement was taken as the diameter of the emerging retinal vessels.[18] The optic disc grading was performed, according to a standardized protocol, by 1 experienced ophthalmologist (SCL).

Automated perimetry (SITA FAST 24-2 program, Humphrey Visual Field Analyzer II, Carl Zeiss Meditec, Dublin, CA) was performed with near refractive correction by trained study technicians on (1) 1 in 5 consecutive non–glaucoma-suspect participants (641 persons) before the ophthalmic examination and (2) all glaucoma-suspect participants (definition below). The visual field test was repeated on another occasion without pupil dilation if the test reliability criteria were not satisfied (fixation losses >20%, false-positives >33%, or false-negatives >33%) or there was a visual field defect (definition below). Data from the normal eyes were used to define the 97.5 and 99.5 percentiles for VCDR, VCDR asymmetry, and IOP in this population.

Diagnostic Definitions

"Glaucoma suspects" were defined as those participants with any of the following criteria: (1) IOP >21 mm Hg, (2) VCDR >0.6 or VCDR asymmetry >0.2, (3) abnormal anterior segment signs consistent with pseudoexfoliation or pigment dispersion syndrome, (4) narrow angles (see below for definition), (5) peripheral anterior synechiae or other findings consistent with secondary glaucoma, and (6) known history of glaucoma. As indicated, these participants underwent gonioscopy, visual field testing, and a repeated IOP measurement, usually on another day.[4]

"Glaucoma cases" were defined according to the International Society for Geographic and Epidemiological Ophthalmology (ISGEO) criteria based on 3 categories.[19] Category 1 cases were defined as glaucomatous optic disc abnormality (VCDR or VCDR asymmetry $\geq$97.5th percentile, or neuroretinal rim width between 11 and 1 o'clock or 5 and 7 o'clock <0.1 VCDR) with a corresponding glaucomatous visual field defect (see below). Category 2 cases were defined as severely damaged optic disc (VCDR or VCDR asymmetry $\geq$99.5th percentile) in the absence of a visual field test. In diagnosing category 1 or 2 glaucoma, it was required that there was no other explanation for the VCDR finding (e.g., dysplastic discs or marked anisometropia) or visual field defect (e.g., retinal vascular disease, macular degeneration, or cerebrovascular diseases). Category 3 cases were defined as subjects without visual field or optic disc data who were blind (corrected visual acuity, <3/60) and had previous glaucoma surgery or an IOP >99.5th percentile.

A glaucomatous visual field defect was defined if the following were found: (1) glaucoma hemifield test outside normal limits and (2) a cluster of 3 or more, non-edge, contiguous points on the pattern deviation plot, not crossing the horizontal meridian with a probability of less than 5% being present in age-matched normals, present on 2 separate occasions.[20] The severity of visual damage was classified using the glaucoma staging system 2 (GSS 2).[21] This method is based on the use of both mean deviation and pattern standard deviation values. The GSS 2 has been shown to correctly classify damage severity and was highly associated with the Advanced Glaucoma Intervention Study score.[21]

A narrow anterior chamber angle was diagnosed if the posterior trabecular meshwork was seen for 180 degrees or less of the angle circumference during static gonioscopy.[4] Primary angle closure glaucoma was defined as an eye with narrow angles and evidence of glaucoma as defined previously. Final definition, adjudication, and classification of glaucoma cases were reviewed by the senior author (TA).[20]

In the current study, we identified bilaterally normal eyes from the subset of SiMES participants who had bilaterally normal visual field tests and excluded individuals classified as glaucoma suspects or those with unreliable visual field results.

Imaging and Analysis with Heidelberg Retina Tomograph II

The HRT II measurements were performed on study subjects after pupil dilation by 2 operators. The HRT cylindrical lenses were adapted for subjects who had astigmatism $\geq$1.0 diopter. After the baseline image was captured, the optic disc margin was manually