



## Assessment of a Race-Specific Normative HRT-III Database to Differentiate Glaucomatous from Normal Eyes in Pakistani Population.

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### **A**bstract

**Purpose:** To determine if a new, normative, race-specific database (Indian Module) enhances the ability of confocal scanning laser ophthalmoscopy in differentiating normal from glaucomatous eyes as compared to the default module setting that uses the Caucasian database.

**Methods and Main Outcome Measure:** A record of 10 subjects was selected for seeing the changes, if any, after adjusting the new normative databases. Other necessary information was obtained where necessary. The detailed printed reports of the subjects were used for record keeping.

**Results:** Almost every eye tested having Optic nerve head marked outside normal limits was either changed to normal Moorfields regression analysis (MRA) result or at least borderline after adjusting for the particular race i.e. Indian. A discrepancy was always noted between the two database results Conclusion: Although the size of the sample data was small yet it established the fact that although the new normative database greatly reduces the false positive error yet the size of the normative database needs to be increased so as to increase the sensitivity while maintaining the high level of specificity as already has been done for the Caucasian database.



## INTRODUCTION

Glaucoma is a disease of the eye marked by increased pressure within the eyeball that can result in damage to the optic disk and gradual loss of vision.<sup>1</sup>

The detection and monitoring of glaucoma are multifactorial processes traditionally involving several diagnostic modalities, including intraocular pressure measurements, subjective evaluation of the optic nerve head (ONH), and visual field testing. These traditional methods of assessing glaucoma have several key limitations that dictate the need for supplementary approaches.

Intraocular pressure is the major identified risk factor for the development of glaucomatous damage, and lowering intraocular pressure serves to impede the progression of retinal degenerative change. Nevertheless, the high inter-individual variability and the diurnal variation in the intraocular pressure have limited the use of this parameter for the detection of the disease. Moreover, intraocular pressure values do not indicate whether damage has occurred, or to what extent.<sup>2,3,4</sup>

Visualization of the ONH in glaucoma by ophthalmoscopic examination or serial stereoscopic photographs is highly dependent on observer skills, inducing high interobserver and intraobserver variation that affects the utility of this diagnostic modality.<sup>4,5</sup>

Visual field analysis through automated perimetry is a widely used technique that is arguably the gold standard to evaluate glaucomatous neuropathy and to monitor disease progression. Although it is sensitive and specific for detecting functional visual field loss, automated perimetry has several significant limitations.<sup>4</sup> The test requires the subjective input of the tested individual; therefore, it is prone to high short- and long-term fluctuation.

This unavoidable source of error necessitates multiple retesting to improve the reliability of the technique, delaying the recognition of glaucomatous damage.<sup>6</sup> Furthermore; numerous studies have shown that glaucomatous field abnormalities may be preceded by structural changes of the ONH and nerve fiber layer.<sup>4</sup>

Because glaucomatous damage is largely irreversible, it is imperative to identify accurately eyes with early structural changes, because they are at risk for continued injury. Glaucomatous changes to the optic nerve head and RNFL loss often precede achromatic visual field changes, and achromatic visual field defects may only become manifest after a large percentage of retinal ganglion

cells have been damaged.<sup>7-9</sup> As such, early detection of optic nerve damage is of great importance in managing glaucoma. Confocal scanning laser ophthalmoscopy has become an important tool in detecting structural damage of the optic nerve head and RNFL, and this imaging modality may assist in early detection of the disease.

Confocal scanning laser ophthalmoscopy is a real-time imaging technique that is used to produce three-dimensional images of the ONH. It is based on the principle of spot illumination and spot detection. A spot of laser light is projected onto the tissue, and the reflected light is detected by a sensor. The system uses a pair of conjugated pinholes located in front of the light source and the light detector components. This pair ensures that only light reflected from a defined focal plane will reach the light detector. Light reflected from layers above or below the focal plane is not focused to the pinhole, leaving only a small fraction that can pass and be detected. Out-of-focus light is highly suppressed, and the suppression increases rapidly with increasing distance from the focal plane. The device moves the focal plane to acquire sequential images. Reconstructing the series of scans at the various focal planes creates a three dimensional topographic representation of the surface that is scanned.<sup>4</sup>

Confocal scanning laser ophthalmoscopic imaging of the optic nerve head (ONH) has been available commercially for around 15 years in the form of Heidelberg retina tomography (HRT). The operational software has undergone continuous development and refinement throughout this period, third major revision of the HRT operational software (HRT-3) in 2006. The principal goals of ONH imaging are to provide information to assist the user in discriminating between normal and glaucomatous optic discs, and to identify glaucoma progression.<sup>10</sup>

One method of HRT software analysis, starting from HRT2 upgrade, Moorfields regression analysis (MRA), uses a program that compares the subject's optic nerve and RNFL parameters to a normative database of 112 subjects, all of whom were white and had ametropia of less than 6 diopters.<sup>11</sup> Given the variations in optic disc morphology among different ethnicities, questions exist as to whether this database can be applied to blacks and other racial groups.<sup>12</sup>

The original HRT normative database was derived from 349 white individuals for the stereometric parameter database and 112 white individuals for the Moorfields regression analysis (MRA) database.<sup>10</sup>

The original database for derivation of HRT II stereometric parameters consisted of 743 Caucasian eyes.





The database consisted of 349 normal eyes, 192 with early glaucoma, 97 with moderate glaucoma and 105 with advanced glaucoma<sup>13</sup>.

A frequent criticism of the original normative database was the lack of ethnic-specific data, particularly as there are well documented ethnic differences in optic disc appearance, with black individuals having larger optic discs and deeper cups than white individuals<sup>14</sup>. This has been partly addressed in the new software (HRT3), with the inclusion of 215 healthy (non-glaucomatous) African-American eyes from one site (Alabama). The white normative database has also been expanded to include 733 healthy eyes of white individuals. A further database of approximately 100 Indian (South Asian) eyes is now available (software version 3.1) and collection of Hispanic and Asian databases is currently in progress.<sup>10</sup>

It has been shown that for white persons, MRA with the new race-specific database of HRT-III increases sensitivity while maintaining a comparable specificity when compared with the MRA for HRT II. As far as black individuals (Africans) are concerned, MRA with the new HRT III database increases sensitivity but decreases specificity for predicting glaucoma when compared with HRT II.

Sensitivity and specificity for the HRT-II was 71.9% and 95.3%, respectively, for white subjects and 50.0% and 98.6%, respectively, for black subjects. Using the expanded HRT-III database, analysis yielded a sensitivity of 81.3% and specificity of 93.8% for whites and a sensitivity of 71.2% and specificity of 86.1% for blacks. After an adjustment for black ethnicity was made in the HRT-III program, the sensitivity and specificity for blacks was 65.4% and 90.3%, respectively.<sup>15</sup> Same situation might arise when to apply the race specific Indian database in Pakistani population. So there was need of careful scrutiny of this new normative database before use in clinical practice.

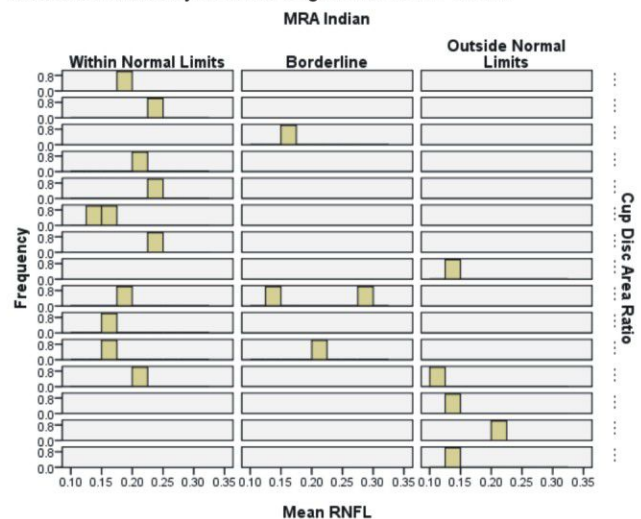
### Results and Discussion:

It is well established that structural changes at the optic nerve head (ONH) are an early and prominent feature of the glaucomatous disease process, so it is to be expected that measurements of ONH structure should be able to distinguish between glaucomatous and healthy nerves. The HRT II derives a large number of measurement parameters, both for the ONH as a whole ("global") and for more localized ONH regions ("predefined segments"). Different mathematical approaches have been applied to the problem of deriving a suitable algorithm that can make best use of all the measurement data to distinguish between normal and glaucomatous eyes. The most frequent approach is to take a

group of healthy non-glaucomatous eyes and a group of glaucomatous eyes and submit all the measurements generated by the HRT to a linear discriminant analysis. The output of such an analysis is a linear combination of the parameters that best distinguish between the two groups.

This approach makes no assumptions about the parameters that are most likely to be useful, but the algorithm derived by the analysis is sensitive to the composition of the two subject groups taken as representative of "normal" and "glaucomatous."<sup>6,7</sup>

An alternative approach is that taken with Moorfields Regression Analysis (MRA). The form of the analysis was derived from a prior knowledge of physiological relationships, i.e., the dependence of neuroretinal rim area on optic disc size, the possibility that neuroretinal rim area may decline with age, and knowledge of the glaucomatous process (e.g., narrowing of the neuroretinal rim). Although narrowing of the rim is said to occur preferentially in some regions of the ONH, it may occur in any region. For this reason, the algorithm was based on an analysis of all segments of the ONH.

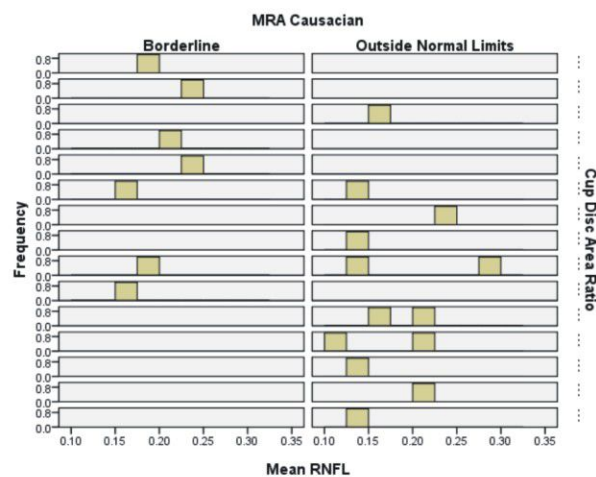


The approach was first applied to planimetry (measurements from ONH photographs and then to HRT images.

So in our practice by using the latest update of HRT3 software Heidelberg Eye Explorer version 3.1 that also constitute a normative database from Indian population the discrepancy among the MRA classification was found in almost every case by using the original Caucasian database (the default option if no normative database is selected) and the new Indian module. Although this greatly reduced the false positive error inherent in the original database but there might be chances of increased false negative errors.



### Relationship of Cup/Disc Area Ratio Mean RNFL and Moorefield Regression Analysis using Caucasian Database



### Relationship of Cup/Disc Area Ratio Mean RNFL and Moorefield

#### Relationship Of Cup/Disc Area Ratio Mean RNFL and Moorefield Regression Analysis using Indian Database

Since visual field defects appear later when about 20 to 40 percent RNFL loss so a comparative study between the new HRT3 normative databases and some sophisticated visual field analyzer like FDT or SWAP needs to be done to further elucidate the situation. As shown by the accompanying tables and graphs discrepancies were more profound when the disc area was greater than  $2.5 \text{ mm}^2$  (normal range being  $1.63$  to  $2.43 \text{ mm}^2$  in Caucasian module and  $1.53$  to  $2.63 \text{ mm}^2$  in the Indian module.)

So my suggestions based on the above factors are

- 1: Carefully select the proper normative database while filling the patient profile before the clinical exam.
- 2: Since MRA classification is based on statistics so never rely upon HRT as a diagnostic tool to discriminate between normal and Glaucomatous ONH especially when the Disc Area is greater than  $3.00 \text{ mm}^2$ . Use it only as an ancillary tool.
- 3: Heidelberg Engineering (Germany) should expand the size of the Indian normative database as it already has done with the Caucasian database that has resulted in increased sensitivity and specificity.
- 4: Further rigorous research is recommended in the same direction including other sophisticated tools like FDT or SWAP.
- 5: The recommendations do not underestimate the utility of this state of the art tool as it is the best tool available today for monitoring the Glaucoma progression.

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