# Combining Multiple HRT Parameters Using the 'Random Forests' Method Improves the Diagnostic Accuracy of Glaucoma in Emmetropic and Highly Myopic Eyes

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**Purpose.** To combine multiple Heidelberg Retina Tomograph (HRT) parameters using the Random Forests classifier to diagnose glaucoma, both in highly and physiologically myopic (highly myopic) eyes and emmetropic eyes.

**Methods.** Subjects consisted of healthy subjects and age-matched patients with open-angle glaucoma in emmetropic (−1.0 to +1.0 diopters [D], 63 and 59 subjects, respectively) and highly myopic eyes (−10.0 to −5.0 D, 56 and 64 subjects, respectively). First, area under the receiver operating characteristic curve (AUC) was derived using 84 HRT global and sectorial parameters and the representative HRT raw parameter (largest AUC) was identified. Then, the Random Forests method was carried out using age, refractive error, and 84 HRT parameters. The AUCs were also derived using the following: (1) Frederick S. Mikelberg discriminant function (FSM) score, (2) Reinhard O.W. Burk discriminant function (RB) score, (3) Moorfields regression analysis (MRA) score, and (4) glaucoma probability score (GPS).

**Results.** In combined emmetropic and highly myopic population, AUC with Random Forests method (0.96) was significantly larger than AUCs with the representative HRT raw parameter (vertical cup-to-disc ratio [global], 0.89), FSM (0.90), RB (0.83), MRA (0.87), and GPS (0.81) ($P < 0.001$). Similarly, AUC with the Random Forests method was significantly ($P < 0.05$) larger than these other parameters, both in emmetropic and highly myopic groups. Also, the Random Forests method achieved partial AUCs above 80%/90% significantly ($P < 0.05$) larger than any other HRT parameters in all populations.

**Conclusions.** Evaluating multiple HRT parameters using the Random Forests classifier provided accurate diagnosis of glaucoma, both in emmetropic and highly myopic eyes.

Keywords: Heidelberg retina tomograph, Random Forests, glaucoma

Glaucoma is the second most common cause of blindness worldwide.[1] Since glaucomatous visual field (VF) damage is irreversible, early diagnosis of glaucoma is essential. Structural changes at the optic nerve head (ONH)[2–4] and retinal nerve fiber layer (RNFL) around the optic disc[5–7] can also indicate glaucomatous damage, and may precede measurable VF loss. Optic nerve head morphology can be imaged using the Heidelberg Retina Tomograph (HRT; Heidelberg Engineering GmbH, Heidelberg, Germany) and it has been reported it is useful to use HRT in screening for glaucomatous eyes.[8–13]

Previous epidemiologic studies have reported myopia is correlated with a high prevalence of open-angle glaucoma (OAG).[14–18] In highly and physiologically myopic (highly myopic) eyes, it is often clinically difficult to diagnose glaucoma using funduscopy, fundus photographs, or imaging devices, including HRT, because optic discs are apparently different from those of emmetropic eyes, both morphologically and histologically. In particular, tilting of the ONH and/or thinning of the RNFL is associated with myopia.[19,20] Indeed, subjects with high myopia are usually excluded from most clinical studies to investigate the usefulness of imaging devices. Hence, there is a limited number of reports that investigated the diagnostic ability of imaging devices in detecting glaucoma in myopic eyes. However, there is one study that investigated the clinical usefulness of HRT in myopic eyes in diagnosing glaucoma. In this study, the diagnostic accuracy was lower in myopic subjects than in emmetropic subjects.[21] This is especially important for Asians, including Japanese, and in patients of Asian origin, because myopia is a common ocular pathology.[22–24]

In glaucoma, there are typical patterns of the morphologic change at the optic disc.[25] Nonetheless previous studies usually simply interpreted different HRT measurements independently.[8–13] Decision tree classifier is one of the pattern recognition methods and it can be considered as a tree-like representation of finite sets of "if-then-else" rules.[26] Once a decision tree classifier is developed using a learning dataset, it can give a prediction of the classification of a separate dataset from the pattern of multiple variables. However, this method suffers from the problem of 'overfitting', which has the influence on

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the diagnostic accuracy.[27] On the other hand, the Random Forests classifier[28] is a decision support tool, which consists of many decision trees and outputs the averaged value of all the individual trees. Each tree is constructed using a different bootstrap sample from the original data; thus, cross-validation is performed internally and the Random Forests method is free from the problem of overfitting. Another particular merit of the Random Forests method is that any correlation between predictor variables can be taken into account and the relationship among the parameters will not bias the results and as a result, predictors that might be overlooked with other methods can contribute to the prediction.[29] Indeed, it has been used to explore interactions between different predictor variables in previous research.[29–31] Thus, the Random Forests method should be particularly useful in diagnosing glaucoma by analyzing multiple HRT parameters that are correlated with each other.

The purpose of this study was to investigate the usefulness of the Random Forests algorithm with HRT parameters in diagnosing glaucoma, both in myopic and emmetropic eyes. For this purpose, OAG patients with emmetropia and high myopia were recruited prospectively, as well as age-matched, nonglaucoma control groups with emmetropia and high myopia. The diagnostic accuracy of interpreting multiple HRT parameters with the Random Forests method was compared with those of HRT raw parameters and other HRT built-in parameters: Frederick S. Mikelberg (FSM) discriminant function,[32] Reinhard O.W. Burk (RB) discriminant function (HRT II Operating Instructions, Dossenheim, Germany), Moorfields regression analysis (MRA),[10] and Glaucoma probability score (GPS).[9]

## METHODS

### Subjects

Data from healthy subjects and OAG patients were prospectively acquired at three institutes in Japan, the University of Tokyo (Tokyo, Japan), Tajimi Municipal Hospital (Gifu, Japan), and Miyata Eye Hospital (Miyazaki, Japan), from the subjects who visited any of the above institutes between January 2007 and December 2008. The study protocol was approved by the institutional review board of each institution and adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from each subject after explanation of the study protocol.

Self-reported healthy volunteers or subjects who visited the institutions for prescriptions for glasses and were at least 20 years of age were invited to participate in the study. The following ocular examinations were performed at the first visit: refraction and best-corrected visual acuity (BCVA) measurements using the 5-m Landolt chart, slit-lamp examination, IOP measurement using a Goldmann applanation tonometer, dilated funduscopy, and VF testing using the Humphrey Field Analyzer 24-2 SITA standard program (HFA; Carl Zeiss Meditec, Inc., Dublin, CA, USA). Those with spherical equivalent refractive errors of −1.0 to +1.0 diopter (D) were assigned to the emmetropic group and those with −10.0 to −5.0 D were assigned to the highly and physiologically myopic (highly myopic) group. Eyes with aberrant disc morphology and/or with pathologic myopic findings on fundus were carefully excluded.

Exclusion criteria were contraindication to pupil dilation, IOP of 22 mm Hg or higher, BCVA worse than 0.7, unreliable results of HFA (fixation loss, false-positive, or false-negative > 20%), glaucomatous VF defects according to Anderson and Patella's criteria as described below,[33] any abnormal VF loss consistent with ocular disease, history of intraocular or refractive surgery, history of ocular or systemic diseases that could affect the results of confocal scanning laser ophthalmoscopy examinations, including clinically significant cataract, any retinal diseases including diabetic retinopathy/maculopathy or AMD, and optic nerve or RNFL abnormality.

Open-angle glaucoma patients from each institution fulfilling the following criteria were also included in this study. The inclusion criteria were: reproducible glaucomatous changes in the ONH with/without RNFL defect as confirmed by a glaucoma specialist (MA, AI, and SO), glaucomatous VF defects as shown by the HFA 24-2 SITA standard program obtained within 3 months of the HRT examination, mean deviation (MD) of the HFA 24-2 SITA standard program greater than −10 dB in at least one eye, and absence of history of other ocular pathologic changes that could affect the results of HFA or HRT examinations, including intraocular surgeries or refractive surgeries. Glaucomatous VF defects were defined according to Anderson and Patella's criteria as follows: cluster of three or more points in the pattern deviation plot within a single hemifield (superior or inferior) with $P$ values less than 5%, one of which must have a $P$ value less than 1%[33] and/or Glaucoma Hemifield Test results outside normal limits and/or abnormal pattern SD with $P$ less than 5%. Patients with refractive errors of −1.0 to +1.0 D were assigned to the emmetropic group and those with −10.0 to −5.0 D were assigned to the highly myopic group. Eyes with aberrant disc morphology or anomaly, or signs suggestive of pathologic myopia were also carefully excluded.

If a nonglaucomatous subject fulfilled the inclusion criteria bilaterally, one randomly chosen eye was included, and if a nonglaucoma subject or an OAG subject fulfilled the inclusion criteria unilaterally, that eye was included in the study. If an OAG patient fulfilled the criteria bilaterally, the eye with worse MD of the HFA 24-2 program was included.

### HRT Measurements

The ONH morphology was evaluated by HRT II using the version 3.0 software as previously reported.[34] Five images were continuously taken, and mean topography images were calculated using three of the five images stored in each measurement. Standard deviations of the integrated images of less than 30 μm were used. A disc contour line was determined by a well experienced operator (TT) for all images with reference to the fundus photographs taken simultaneously. The standard reference plane was 50-μm posterior to the mean height of the disk contour, located temporally between 350° and 356°.

### Statistical Analyses

Receiver operating characteristic (ROC) curve and area under the curve (AUC) were calculated using 84 raw values of global and sectorial HRT parameters (Table 1) and the parameter with the largest AUC was identified, in combined emmetropic and myopic group and also in these groups separately (representative HRT raw parameter). The FSM discriminant function,[32] RB discriminant function (Heidelberg Retina Tomograph II Operating Instructions), results of MRA[10] and GPS[9] were automatically calculated in the apparatus. First, using these results, AUCs were compared between the Random Forests method and the representative HRT raw parameter, FSM, MRA, and RB in the combined emmetropic and myopic group. Then, similar analysis was carried out in each of the two groups, respectively, as a subclass analysis.

A GPS score was calculated by importing the HRT data obtained with the HRT II into the HRT III. As one of the

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**Table 1.** Heidelberg Retina Tomograph Parameters Used in the Random Forest Algorithm

| |
|---|
| Seven global indices |
| Horizontal cup-to-disk ratio |
| Vertical cup-to-disk ratio |
| Maximum contour elevation |
| Maximum contour depression |
| CLM temporal superior |
| CLM temporal inferior |
| Average variability (SD) |
| Eleven global indices and values in six sectors |
| Disc area |
| Rim area |
| Cup-to-disk area ratio |
| Cup volume |
| Rim volume |
| Mean cup depth |
| Maximum cup depth |
| Height variation contour |
| Cup shape measure |
| Mean RNFL thickness |
| RNFL cross-sectional area |

institutes was equipped only with HRT II, GPS data was not available for the patient in that institute. Hence, the comparison of AUC between the GPS and the Random Forests method was performed using the subjects whose GPS data were available. First, using these results, AUCs were compared between the Random Forests method and corresponding GPS scores in the combined emmetropic and myopic group. Then, similar analysis was carried out in each of the two groups, respectively, as a subclass analysis.

The Random Forests method was also used to classify glaucoma and healthy eyes with 84 HRT parameters (Table 1). In this procedure, 10,000 trees were grown to form the Random Forests diagnosing system, followed by confirmation whether further increasing the number of trees does not lead to additional improvement of diagnostic accuracy. Receiver operating characteristic curves and AUCs were derived from the probability of glaucoma (the proportion of votes) as suggested by the method; for each individual, only the data from all other subjects was used to create the Random Forests diagnosing system and the remaining one eye was used as a testing dataset (leave-one-out cross validation).[35] The five most important parameters were decided by calculating the total decrease in node impurities by permuting the each variable in each tree and observing the decrease of the Gini index normalized by the SD of the difference.[28] The Gini index is a measure of partition purity and decision tree is built by finding split-point with minimum Gini index.[27]

All statistical analyses were carried out using the statistical programming language R (ver. 2.14.2; The R Foundation for Statistical Computing, Vienna, Austria) and Medcalc version 11.4.2.0; MedCalc statistical software, Mariakerke, Belgium). The R package 'randomForest' was used to carry out the analysis of the Random Forests method and the comparison of total AUCs were carried out using the DeLong method.[36] The AUC was used to evaluate the clinical usefulness of classifier, as suggested in a previous paper.[37] In the current study, partial AUCs above 80% and 90% associated with each method were compared, in addition to the total AUC, using the bootstrap method.[38,39] The Holm's method[40,41] was used to correct the $P$ values in multiple testing ($P < 0.05$).

## Results

There were 63 emmetropic eyes of 63 healthy subjects, 59 emmetropic eyes of 59 OAG patients, 56 highly myopic eyes of 56 healthy subjects, and 64 highly myopic eyes of 64 OAG patients enrolled in the study. Demographic data of the subjects are summarized in Table 2. Age and refractive error showed no significant difference between control and glaucoma subjects in both emmetropic and highly myopic groups (nonpaired $t$-test, $P \geq 0.05$).

In the Random Forests, much less than 10,000 trees (less than 4000 trees in the combined emmetropic and myopic group and myopic group and less than 2000 trees in the emmetropic group) were needed for the error rate to be saturated. This means the diagnostic accuracy does not further improve by increasing the number of the trees.

In combined emmetropic and highly myopic population, the representative HRT raw parameter was the vertical cup-to-disc ratio (global) (0.89 [confidence interval (CI): 0.84–0.93], Fig. 1). The ROC curves of FSM, RB, and MRA for this population were shown in Figure 1. The AUCs associated with FSM, RB, and MRA were 0.90 (CI: 0.85–0.93), 0.83 (CI: 0.77–0.88), and 0.87 (CI: 0.82–0.91), respectively. The AUC associated with the Random Forests method was 0.96 (CI: 0.93–0.98), which was significantly larger than others (against representative HRT raw parameter: $P < 0.001$, FSM: $P < 0.001$, RB: <0.001, and MRA: $P < 0.001$, all of the $P$ values were significant after the correction for multiple testing using the Holm's method[40,41]).

The representative HRT raw parameter was the cup-to-disc area ratio in the inferior-temporal sector in the emmetripic eyes (AUC = 0.95 [CI: 0.90–1.0], Fig. 2a) and vertical cup-to-disc ratio (global) in the highly myopic eyes (AUC = 0.85 [CI: 0.77–0.91], Fig. 3a). The ROC curves of FSM, RB, and MRA for emmetropic and highly myopic eyes were shown in Figures 2a and 3a, respectively. The AUCs of the three methods were 0.93 (95% CI: 0.88–0.97), 0.90 (CI: 0.85–0.96), and 0.93 (CI: 0.89–0.98) in emmetropic eyes, respectively, while these were 0.86 (CI: 0.78–0.92), 0.75 (CI: 0.66–0.84), and 0.79 (CI: 0.70–0.86) in highly myopic eyes. The AUCs associated with the Random Forests method (0.98 [CI: 0.96–1.0] in emmetropic group and 0.93 [CI: 0.88–0.97] in highly myopic group) were significantly larger than those with other parameters both in emmetropic and highly myopic eyes ($P = 0.0498$ for representative HRT raw parameter, $P = 0.004$ for FSM, $P = 0.001$ for RB, and $P = 0.003$ for MRA in the emmetropic group, and $P = 0.006$ for representative HRT raw parameter, $P = 0.009$ for FSM, and $P < 0.001$ for RB, and $P < 0.001$ for MRA in the highly myopic group, all of the $P$ values were significant after the correction for multiple testing using the Holm's method[40,41]). The five most contributing parameters in the Random Forests diagnosing system in the emmetropic and highly myopic groups were shown in Figures 2b and 3b, respectively.

Glaucoma probability score data were not available in 1 (emmetropic normal group), 4 (highly myopic normal group), 19 (emmetropic glaucomatous group) and 1 eye(s) (emmetropic highly myopic group). As a result, global GPS score was obtained in 62 emmetropic healthy eyes, 55 emmetropic eyes with glaucoma, 37 highly myopic healthy eyes, and 63 highly myopic eyes with glaucoma (Table 2). In this population, age and refractive error showed no significant difference between control and glaucoma subjects in both emmetropic and highly myopic groups (nonpaired $t$-test, $P > 0.05$). As shown in the Table 3, the AUC associated with the Random Forests method (0.96 [CI: 0.94–0.98]) were significantly larger than those of the corresponding global GPS score (0.81 [CI: 0.75–0.86], in the combined emmetropic and highly myopic group [$P < 0.001$]). In addition, the AUCs associated with the Random

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**Table 2.** Subject Demographics

| | Original Subjects | | | | | Subjects for the Global GPS Analysis | | | | | Subjects for the Sectorial GPS Analysis | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N (Male/Female) | Age, y | Refraction, D | MD, dB | IOP, mm Hg | N (Male/Female) | Age, y | Refraction, D | MD, dB | IOP, mm Hg | N (Male/Female) | Age, y | Refraction, D | MD, dB | IOP, mm Hg |
| Emmetropic eyes | | | | | | | | | | | | | | | |
| Healthy | 63 (30/33) | 60.0 ± 5.2 | 0.2 ± 0.5 | −0.5 ± 1.1 | 13.2 ± 2.3 | 62 (30/32) | 59.8 ± 5.2 | 0.2 ± 0.5 | −0.5 ± 1.1 | 13.1 ± 2.2 | 60 (29/31) | 59.7 ± 5.2 | 0.2 ± 0.5 | −0.5 ± 1.1 | 12.9 ± 1.8 |
| Glaucoma | 59 (12/47) | 61.7 ± 10.3 | 0.0 ± 0.6 | −4.0 ± 2.0 | 14.5 ± 3.5 | 55 (11/44) | 61.0 ± 10.2 | 0.0 ± 0.6 | −4.1 ± 2.0 | 14.3 ± 3.2 | 51 (11/40) | 60.5 ± 10.4 | 0.0 ± 0.6 | −4.2 ± 2.0 | 14.2 ± 3.3 |
| Highly myopic eyes | | | | | | | | | | | | | | | |
| Healthy | 56 (26/30) | 38.7 ± 11.6 | −7.3 ± 1.5 | −1.3 ± 1.1 | 13.4 ± 1.9 | 37 (17/20) | 39.6 ± 11.8 | −7.3 ± 1.5 | −1.3 ± 1.2 | 13.7 ± 1.9 | 35 (15/20) | 39.2 ± 11.7 | −7.2 ± 1.5 | −1.2 ± 1.1 | 13.7 ± 1.9 |
| Glaucoma | 64 (32/32) | 41.0 ± 6.4 | −7.5 ± 1.7 | −4.2 ± 2.3 | 14.6 ± 2.6 | 63 (31/32) | 41.3 ± 6.1 | −7.3 ± 1.5 | −4.1 ± 2.2 | 14.7 ± 2.6 | 62 (31/31) | 41.5 ± 6.0 | −7.3 ± 1.5 | −4.0 ± 2.2 | 14.7 ± 2.6 |

Age and refractive error showed no significant difference between control and glaucoma subjects within both emmetropic and highly myopic groups (nonpaired *t*-test, $P \geq 0.05$). N, number of eyes; refraction, spherical equivalent refractive error; MD, mean deviation (Humphrey Field Analyzer, 24-2 SITA standard).

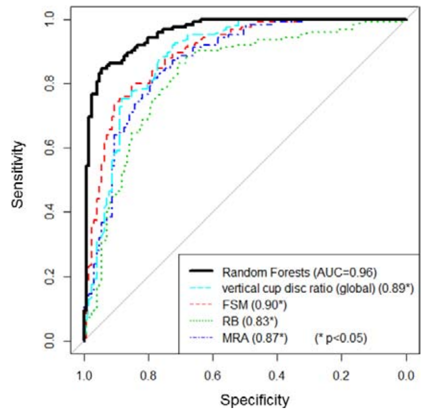


**Figure 1.** Receiver operating characteristic curves for diagnosing glaucoma and five most contributing HRT parameters in mixture of emmetropic and highly and physiologically myopic eyes ($n = 242$). The AUC associated with the Random Forests method was significantly larger than those with FSM, RB, MRA, and the representative HRT raw parameter (vertical cup-to-disc ratio [global]; DeLong's method, $P < 0.05$. All of the $P$ values were significant after the correction for multiple testing using the Holm's method[40,41]). The five most important parameters were decided by calculating the total decrease in node impurities by permuting the each variable in each tree and observing the decrease of the Gini index followed by normalizing by the SD of the difference. *Significantly smaller than AUC values given by Random Forests method (using the DeLong's method, $P < 0.05$).

Forests method (0.98 [CI: 0.96–1.0] in the emmetropic group and 0.93 [CI: 0.88–0.98] in the highly myopic group) were significantly larger than those of the corresponding global GPS score (0.88 [CI: 0.82–0.94] in the emmetropic group [$P = 0.001$] and 0.80 [CI: 0.71–0.89] in the highly myopic group [$P = 0.007$]).

Sectorial GPS score was not calculated in two emmetropic healthy eyes, four emmetropic eyes with glaucoma, two highly myopic healthy eyes, and one highly myopic eye with glaucoma. As a result, sectorial GPS scores were obtained in 60 emmetropic healthy eyes, 51 emmetropic eyes with glaucoma, 35 highly myopic healthy eyes, and 62 highly myopic eyes with glaucoma (Table 2). In this population, age and refractive error showed no significant difference between control and glaucoma subjects in both emmetropic and highly myopic groups (nonpaired *t*-test, $P > 0.05$). As shown in the Table 3, the AUC associated with the Random Forests method (0.96 [CI: 0.94–0.99]) in the combined emmetropic and highly myopic group was significantly larger than those of other corresponding sectorial GPS scores, (AUCs: 0.78–0.79 in emmetropic group and 0.76–0.80 in the highly myopic group, $P < 0.001$, all of the $P$ values were significant after the correction for multiple testing using the Holm's method[40,41]). In addition, the AUCs associated with the Random Forests method (0.98 [CI: 0.96–1.0]) in the emmetropic group (0.94 [CI: 0.89–0.98]) and in the highly myopic group (0.97 [CI: 0.94–0.99]) were significantly larger than those of other corresponding sectorial GPS scores (AUCs: 0.87–0.89 in emmetropic group and 0.76–0.80 in the highly myopic group, $P$ values were between <0.001 and 0.004 in the emmetropic group and between <0.001 and 0.009 in the highly myopic group, all of the $P$ values were significant after the correction for multiple testing using the Holm's method[40,41]).

The comparisons of the partial AUCs are depicted in the Table 4. The AUCs associated with the Random Forests method was significantly larger than any other parameters at the specificity between 90% and 100%, in combined emmetropic and highly myopic groups and also in both of the emmetropic

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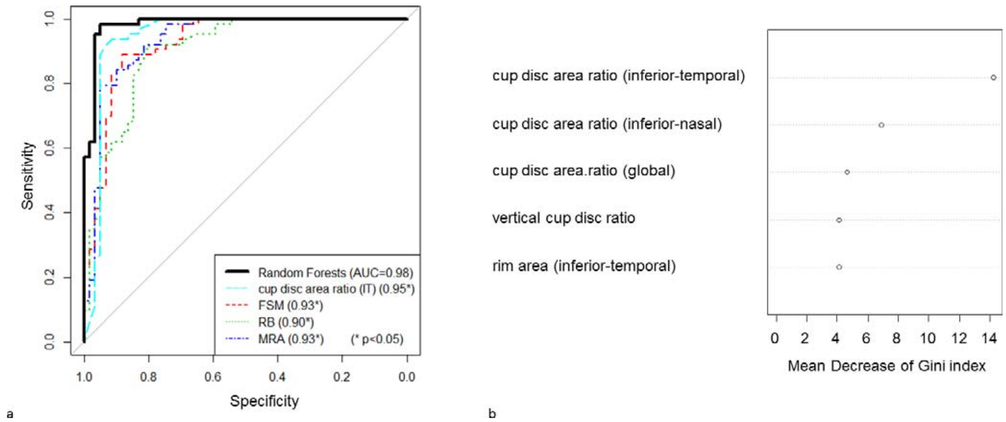


**FIGURE 2.** Receiver operating characteristic curves for diagnosing glaucoma and five most contributing HRT parameters in emmetropic eyes ($n =$ 122). (**a**) Receiver operating characteristic curves and (**b**) the five most contributing HRT parameters in the Random Forests diagnosing system. The AUC associated with the Random Forests method was significantly larger than those with FSM, RB, MRA, and the representative HRT raw parameter (cup-to-disc area ratio in the inferior-temporal sector; DeLong's method, $P < 0.05$. All of the $P$ values were significant after the correction for multiple testing using the Holm's method[40,41]). The five most important parameters were decided by calculating the total decrease in node impurities by permuting the each variable in each tree and observing the decrease of the Gini index followed by normalizing by the SD of the difference. *Significantly smaller than AUC values given by Random Forests method (using the DeLong's method, $P < 0.05$: actual $P$ values are described in the main text).

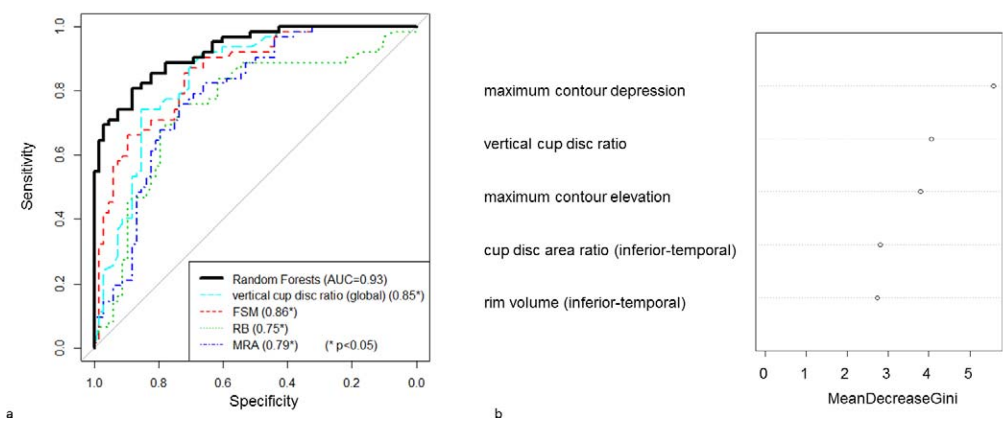


**FIGURE 3.** Receiver operating characteristic curves for diagnosing glaucoma and five most contributing HRT parameters in highly and physiologically myopic eyes ($n = 120$). (**a**) Receiver operating characteristic curves and (**b**) the five most contributing HRT parameters in the Random Forests diagnosing system. The AUC associated with the Random Forests method was significantly larger than those with FSM, RB, MRA, and the representative HRT raw parameter (vertical cup-to-disc ratio [global]; DeLong's method, $P < 0.05$. All of the $P$ values were significant after the correction for multiple testing using the Holm's method[40,41]). The five most important parameters were decided by calculating the total decrease in node impurities by permuting the each variable in each tree and observing the decrease of the Gini index followed by normalizing by the SD of the difference. *Significantly smaller than AUC values given by Random Forests method (using the DeLong's method, $P < 0.05$: actual $P$ values are described in the main text).

**TABLE 3.** The Comparison Between AUCs Associated With the Random Forest Method and GPS in Combined Emmetropic and in the Highly Myopic Group, Emmetropic Group, and Highly Myopic Group

| | Emmetropic and Highly Myopic Eyes | | Emmetropic Eyes | | Highly Myopic Eyes | |
|---|---|---|---|---|---|---|
| | *N*, eyes | AUC (CI) | *N*, eyes | AUC (CI) | *N*, eyes | AUC (CI) |
| Random Forest | 217 | 0.96 (0.94–0.98) | 117 | 0.98 (0.96–1.0) | 100 | 0.93 (0.88–0.98) |
| GPS (global) | 217 | 0.81 (0.75–0.86)* | 117 | 0.88 (0.82–0.94)* | 100 | 0.80 (0.71–0.89)* |
| Random Forest | 208 | 0.96 (0.94–0.99)* | 111 | 0.98 (0.96–1.00)* | 97 | 0.93 (0.87–0.98)* |
| GPS (temporal) | 208 | 0.79 (0.73–0.85)* | 111 | 0.87 (0.80–0.94)* | 97 | 0.79 (0.70–0.89)* |
| GPS (nasal) | 208 | 0.79 (0.74–0.85)* | 111 | 0.87 (0.80–0.94)* | 97 | 0.80 (0.71–0.89)* |
| GPS (superior-temporal) | 208 | 0.82 (0.76–0.87)* | 111 | 0.89 (0.83–0.95)* | 97 | 0.78 (0.69–0.88)* |
| GPS (inferior-temporal) | 208 | 0.78 (0.72–0.84)* | 111 | 0.87 (0.80–0.93)* | 97 | 0.76 (0.66–0.86)* |
| GPS (superior-nasal) | 208 | 0.80 (0.74–0.86)* | 111 | 0.87 (0.80–0.94)* | 97 | 0.79 (0.69–0.88)* |
| GPS (inferior-nasal) | 208 | 0.81 (0.75–0.86)* | 111 | 0.88 (0.81–0.95)* | 97 | 0.79 (0.70–0.89)* |

* $P < 0.05$ for the difference between the AUCs associated with the Random Forests method and each parameter using the DeLong's method. All of the $P$ values were significant after the correction for multiple testing using the Holm's method.[40,41]



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**Table 4.** The Comparison Between Partial AUCs Associated With the Random Forest Method and Other HRT Parameters

| Method | Combined Emmetropic and Highly Myopic Group | | | | | Emmetropic Group | | | | | Highly Myopic Group | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *N* | pAUC, 90% | *P* Value | pAUC, 80% | *P* Value | *N* | pAUC, 90% | *P* Value | pAUC, 80% | *P* Value | *N* | pAUC, 90% | *P* Value | pAUC, 80% | *P* Value |
| Random Forests | 242 | 0.074 | | 0.16 | | 122 | 0.087 | | 0.18 | | 120 | 0.068 | | 0.15 | |
| FSM | 242 | 0.045 | 0.003 | 0.12 | 0.0005 | 122 | 0.048 | 0.0014 | 0.136 | 0.0017 | 120 | 0.042 | 0.0071 | 0.11 | 0.003 |
| RB | 242 | 0.023 | <0.001 | 0.083 | <0.001 | 122 | 0.043 | 0.001 | 0.12 | <0.001 | 120 | 0.011 | <0.001 | 0.06 | <0.001 |
| MRA | 242 | 0.0306 | <0.001 | 0.1 | <0.001 | 122 | 0.0525 | 0.004 | 0.139 | 0.007 | 120 | 0.015 | <0.001 | 0.061 | <0.001 |
| Vertical cup-to-disc ratio (global) | 242 | 0.0307 | <0.001 | 0.11 | <0.001 | 122 | 0.0518 | 0.0038 | 0.15 | 0.004 | 120 | 0.024 | <0.001 | 0.086 | 0.0012 |
| Random Forests | 217 | 0.074 | | 0.17 | | 117 | 0.083 | | 0.18 | | 100 | 0.066 | | 0.15 | |
| GPS (global) | 217 | 0.01 | 0.001 | 0.091 | <0.001 | 117 | 0.041 | <0.001 | 0.1 | <0.001 | 100 | 0.039 | 0.01 | 0.094 | 0.003 |
| Random Forests | 208 | 0.075 | | 0.17 | | 111 | 0.082 | | 0.18 | | 97 | 0.069 | | 0.15 | |
| GPS (temporal) | 208 | 0.036 | <0.001 | 0.0853 | <0.001 | 111 | 0.035 | <0.001 | 0.087 | <0.001 | 97 | 0.038 | 0.0045 | 0.094 | 0.009 |
| GPS (nasal) | 208 | 0.04 | <0.001 | 0.088 | <0.001 | 111 | 0.0378 | <0.001 | 0.0891 | <0.001 | 97 | 0.042 | 0.013 | 0.097 | 0.009 |
| GPS (superior-temporal) | 208 | 0.034 | <0.001 | 0.0845 | <0.001 | 111 | 0.039 | 0.0012 | 0.11 | 0.0013 | 97 | 0.027 | <0.001 | 0.08 | 0.002 |
| GPS (inferior-temporal) | 208 | 0.035 | <0.001 | 0.081 | <0.001 | 111 | 0.0379 | <0.001 | 0.0888 | <0.001 | 97 | 0.03 | <0.001 | 0.08 | <0.001 |
| GPS (superior-nasal) | 208 | 0.037 | <0.001 | 0.087 | <0.001 | 111 | 0.04 | 0.0012 | 0.091 | <0.001 | 97 | 0.033 | 0.0006 | 0.088 | 0.003 |
| GPS (inferior-nasal) | 208 | 0.041 | <0.001 | 0.091 | <0.001 | 111 | 0.041 | 0.0019 | 0.093 | <0.001 | 97 | 0.042 | 0.011 | 0.097 | 0.009 |

*P* values were calculated for the difference between the pAUCs associated with the Random Forests method and each parameter using the bootstrap method. All of the *P* values were significant after the correction for multiple testing using the Holm's method.[40,41] pAUC, partial area under the receiver operating characteristic curve.

and highly myopic groups (comparison of the partial AUC was carried out using bootstrap method: $P < 0.001$, all of the $P$ values were significant after the correction for multiple testing using the Holm's method[40,41]). Similarly, the AUCs associated with the Random Forests method was significantly larger than any other parameters at the specificity between 80% and 100%, in (comparison of the partial AUC was carried out using bootstrap method: $P < 0.01$, all of the $P$ values were significant after the correction for multiple testing using the Holm's method[40,41]).

## Discussion

In this study, OAG patients with emmetropia and highly and physiologically myopia (high myopia) were recruited prospectively, as well as age-matched control subjects. Heidelberg Retina Tomograph measurement was carried out in these subjects and the AUCs in diagnosing glaucoma were compared with HRT raw parameters, FSM, RB, MRA, and the Random Forests method. Among the 84 HRT raw parameters, the largest AUC was obtained with different parameters in emmetropic and highly myopic groups and the AUCs in highly myopic eyes became smaller than those in emmetropic eyes. The AUC associated with the Random Forests method in the highly myopic group was smaller than that in the emmetropic group, however, they were significantly larger than those associated with other parameters, in both emmetropic and highly myopic groups. In addition, the AUCs associated with the Random Forests method was significantly larger than any other parameters at the specificity above 80% and 90%, in all of the emmetropic, highly myopic and combined emmetropic and highly myopic groups.

Among 84 HRT raw values, cup-to-disc area ratio (inferior-temporal sector) showed largest AUC in emmetropic eyes. This is in agreement with a previous study[42] and it would be speculated that this is because these areas correspond to VF area, which is preferentially affected in the early stage of glaucoma.[43,44] On the other hand, vertical cup-to-disk ratio (global) showed the largest AUC among HRT raw parameters, in the highly myopic group. Moreover, the two most contributing factors in the Random Forests diagnosing system were sectorial parameters in emmetropic eyes (cup-to-disc area ratio [inferior-temporal] and cup-to-disc area ratio [inferior-nasal]), whereas those in highly myopic eyes were global parameters (maximum contour depression and vertical cup-to-disc ratio). These findings may be compatible with the previous histologic report, in that highly myopic glaucomatous eyes tend to have more diffuse than localized change: elongated shape, shallow and concentric disc cupping, and low frequency of localized RNFL defects.[45]

There are four artificial parameters equipped in the HRT. Frederick S. Mikelberg discriminant function is a linear discriminant function, which uses rim volume, cup shape measure, and height variation contour in the formula.[32] Reinhard O.W. Burk discriminant function uses rim area, height variation contour, cup shape measure, and RNFL thickness (HRT II Operating Instructions). Moorfields regression analysis is also a linear discriminant function, which accounts for the relationship between optic disc size and rim area or cup-to-disc area ratio,[10] and GPS is the result of analysis of automatic stereometric data of the ONH shape using machine learning classifier (relevance vector machine).[9] The sensitivity and specificity of these methods varies according to the study populations. In the original papers, the FSM discriminant function exhibited 0.85 sensitivity and 0.84 specificity[32] and MRA yielded 0.75 sensitivity and 0.98 specificity values.[10] The AUCs associated with FSM, RB, and

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MRA for discriminating glaucomatous and healthy eyes have been reported as 0.76 to 0.86 (FSM), 0.75 to 0.84 (RB), 0.70 to 0.93 (MRA), and 0.88 (GPS).[46–48] The AUCs of these parameters in the emmetropic population of the current study was larger than in these previous studies, despite relatively less damaged in the current study (MD of approximately between –5 and –6 dB in the previous studies). This result could be attributed to the more strict inclusion criteria for the refraction error; it was within ±1 D in the current study, whereas ±5 or 6 D[46,47,49] or mean ± SD equaling –0.01 ± 1.89 D[48] in the previous studies.

In the current study, AUC associated with GPS was similar to those with other three artificial parameters and it was significantly smaller than that with the Random Forests method. This is in agreement with previous reports. The usefulness of GPS is merely similar to,[49–53] or even worse than MRA.[54] In particular, previous reports have reported that GPS was not as useful as MRA and FSM in detecting early glaucoma in Japanese eyes.[55,56] Moreover, it is often clinically experienced that the GPS cannot be calculated, which limits the clinical usefulness of the GPS score. Indeed, in the current study sectorial GPS score was not calculated in six (5.4%) emmetropic eyes and three (3.1%) highly myopic eyes, while this phenomenon does not occur with the Random Forests method. There is an ethnical difference in optic disc appearance[57–64] and the machine learning classifier within the GPS analysis was neither trained in Japanese eyes and in highly myopic population; hence, this may be one of the reasons for the relatively lower performance of GPS than the Random Forests method.

Not surprisingly, the AUC values in the myopic population with the HRT parameters became smaller than those in the emmetropic eyes. Most importantly, the AUC was significantly improved by applying the Random Forests method in both emmetropic and highly myopic groups, as shown in the Figure 2, and the AUC in highly myopic group reached a value of 0.93, which is approximately equivalent to those with HRT raw parameters, FSB, RB, and MRA in emmetropic eyes. It should be noted that the reference plane used in highly myopic eyes would not be identical to that in emmetropic eyes, which would have some impact on the measured HRT parameters in highly myopic eyes (hence, it would not be appropriate to compare the measured HRT parameters directly between emmetropic and highly myopic groups). Although this problem was thought to be at least partly resolved by providing the myopic refraction-matched control group, this could give another explanation to the poor diagnostic performance in the myopic group.

A possible caveat of the current study is the usage of HRT II, instead of III. There was a considerable change between the two versions; for instance, MRA was upgraded in the newest version of software (version 3.0), due to the increase of the number of the subjects included in the normative database.[65] Nonetheless the influence of this change on the diagnostic ability has been reported to be negligible,[49,66] and hence this will not largely affect the results in the current study.

There are other machine learning methods, such as support vector machines, boosting, and bagging classifiers that could also be used to diagnose glaucoma. Previous reports suggest that the Random Forests method outperforms most other methods[67–69]; hence, the Random Forests algorithm was used in the current study.

In the current study, the analysis associated with the Random Forests method was carried out using the leave-one out cross validation in which the original dataset was divided into testing (one patient) and learning (all of other patients) datasets and the Random Forests diagnosis system was developed using the learning dataset. This process was repeated for the number of the subjects in the original dataset so that all of the patients were used as test data once. This is same to the situation of predicting the diagnosis of a new patient (testing dataset) using the Random Forests diagnosis system trained using previous (learning dataset) at a clinical setting. Thus, it was suggested that clinicians can gain the privilege of accurate prediction of the Random Forests diagnosis, when a clinical support tool in which the Random Forests diagnosis system is implemented becomes available at the clinical settings. Thus, given a new glaucoma patient's HRT data set, clinicians should be able to diagnose this patient with known sensitivity and specificity (Figs. 1, 2a, 3) applying the Random Forests diagnosis system currently reported to everyday practice, assuming that a personal computer or other clinical support tools in which the Random Forests diagnosis system is implemented are available. All of the analyses in the current study were carried out using existing statistical software and packages, specifically the language R, which is an open source statistical program.

In conclusion, glaucomatous changes in ONH morphology were investigated based on the HRT parameters of the emmetropic and highly myopic eyes. With any of the parameters, the diagnostic ability was lower in myopic population than in emmetropic population, however, the diagnostic accuracy was improved by interpreting multiple HRT parameters with the Random Forests method, in highly myopic eyes in particular. In Asian countries, the prevalence of high myopia is high,[24,70,71] and high myopia is a definitive risk factor for having glaucoma.[15,72] The current method of using the Random Forests decision tree classifier may be useful in facilitating screening out glaucomatous eyes in these regions.

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