Validation of a Predictive Model to Estimate the Risk of Conversion From Ocular Hypertension to Glaucoma

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Objectives: To develop and validate a predictive model to estimate the risk of conversion from ocular hypertension to glaucoma.

Methods: Predictive models for the 5-year risk of conversion to glaucoma were derived from the results of the Ocular Hypertension Treatment Study (OHTS). The performance of these models was assessed in an independent population of 126 subjects with ocular hypertension from a longitudinal study (Diagnostic Innovations in Glaucoma Study [DIGS]). The performance of the OHTS-derived models was assessed in the DIGS cohort according to equality of regression coefficients, discrimination (*c*-index), and calibration.

Results: Thirty-one patients (25%) developed glaucoma during follow-up. Hazard ratios for DIGS- and OHTS-derived predictive models were similar for age, intraocular pressure, central corneal thickness, vertical cup-disc ratio, and pattern standard deviation but were significantly different for the presence of diabetes mellitus. When applied to the DIGS population, the OHTS-derived predictive models had reasonably good discrimination (*c*-indexes of 0.68 [full model] and 0.73 [reduced model]) and calibration.

Conclusions: The OHTS-derived predictive models performed well in assessing the risk of glaucoma development in an independent population of untreated subjects with ocular hypertension. A risk scoring system was developed that allows calculation of the 5-year risk of glaucoma development for an individual patient.

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RECENT RESULTS FROM THE Ocular Hypertension Treatment Study (OHTS) have established that medical reduction of intraocular pressure (IOP) decreases the risk of progression to glaucoma in patients with ocular hypertension (OHT). After 5 years of follow-up, the cumulative probability of glaucoma development was reported to be 9.5% for untreated patients and 4.4% for patients who received treatment.[1] Although the majority of patients did not develop glaucoma during follow-up, even when left untreated, a stratified analysis according to risk factors showed that the risk of conversion to glaucoma was remarkably variable among different subgroups, being as high as 36% for select patients.[2] The decision to treat a patient with OHT should, therefore, involve an assessment of risk factors for development of glaucomatous damage.[3]

Risk factors such as older age, higher IOP, thinner central corneal thickness (CCT), larger vertical cup-disc ratio measurements, and higher visual field pattern standard deviation (PSD) values have all been identified by the OHTS as significantly associated with an increased risk for glaucoma development. History of diabetes mellitus, on the other hand, was identified as a protective factor in that study. Although the OHTS results have provided a better understanding of the relevant risk factors involved in progression from OHT to glaucoma, clinicians are still faced with the challenge of integrating these factors for a global assessment of the risk for a particular patient. A collective assessment of risk factors using predictive models could help determine who has a higher chance of developing damage and whether to initiate or withhold therapy for a particular subject. Incorporation of these models into clinical practice could increase consistency in patterns of treatment and improve quality of care for patients with OHT.

In the present study, we developed a simplified model for predicting the risk of glaucoma development for a patient with OHT based on published results from the OHTS. For risk models to have optimal use

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and acceptability, clinicians need to be confident that the prediction functions can be transferred to other settings beyond where they were originally derived.[4,5] Therefore, we also present results of the validation of the developed risk models on an independent population of untreated patients with OHT followed up over time.

METHODS

PARTICIPANTS

This observational cohort study included 252 eyes of 126 patients with OHT who were studied without receiving ocular hypotensive treatment during follow-up. All patients were followed up at the Hamilton Glaucoma Center, University of California, San Diego (UCSD) (La Jolla) as part of an ongoing, prospective, longitudinal study (Diagnostic Innovations in Glaucoma Study [DIGS]) initiated in 1988. The overall aims of DIGS were to develop improved methods to detect the onset and progression of structural and functional damage in glaucoma, to evaluate the rate and risk factors for glaucoma development and progression, and to characterize the relationship between structural and functional change over time. Consecutive patients attending the glaucoma clinic at the Hamilton Glaucoma Center UCSD were recruited to participate in the DIGS. After entry in the study, patients in DIGS were longitudinally evaluated according to a preestablished protocol that included regular follow-up visits in which they underwent clinical examination and several other imaging and functional tests. All the data were entered in a computer database, which contained information on 1876 subjects, including healthy subjects, patients with glaucoma, and patients suspected of having glaucoma. For the current study, we retrospectively selected a cohort of untreated patients with OHT from the DIGS population, and clinical information was obtained from our research database. All patients with OHT who met the inclusion criteria described later were enrolled in the current study. Informed consent was obtained from all participants. The UCSD Human Subjects Committee approved all protocols, and the methods described adhere to the tenets of the Declaration of Helsinki and Health Insurance Portability and Accountability Act of 1996 regulations.

Baseline and follow-up examinations consisted of a comprehensive ophthalmologic examination including review of medical history, best-corrected visual acuity, slitlamp biomicroscopy, Goldmann applanation tonometry, gonioscopy, dilated funduscopic examination using a 78-diopter (D) lens, stereoscopic optic disc photography, and visual field examination with standard automated perimetry (SAP). At baseline, SAP testing was performed using program 24-2 (Carl Zeiss Meditec, Dublin, Calif) full-threshold strategy. During follow-up, SAP testing was performed using either full-threshold or Swedish Interactive Threshold Algorithm strategies. All patients also had CCT measurements obtained during follow-up by a trained technician who was masked to the status and other examinations of the patients. For each patient, CCT was calculated as the average of 3 measurements obtained during the same visit using ultrasound pachymetry (Pachette GDH 500; DGH Technology, Inc, Philadelphia, Pa).

To be included, subjects had to have a best-corrected visual acuity of 20/40 or better, spherical refraction within ±5.0 D and cylinder correction within ±3.0 D, and open angles on gonioscopy. Patients with secondary causes of high IOP (eg, pseudoexfoliation, pigment dispersion syndrome, iridocyclitis, trauma), other intraocular eye disease, history of refractive surgery, or other diseases possibly affecting the visual field (eg, demyelinating diseases, pituitary lesions) were excluded. Patients with any evidence of diabetic retinopathy documented from a dilated ophthalmoscopic examination were also excluded from the study.

Evaluation of structural damage to the optic disc at baseline was based on assessment of simultaneous stereoscopic optic disc photographs (TRC-SS; Topcon Instrument Corp of America, Paramus, NJ). Stereoscopic sets of slides were examined using a stereoscopic viewer (Asahi Pentax, Golden, Colo). The photographs were evaluated by 2 experienced graders, and each was masked to the subject's identity and to the other test results. Each grader was previously trained using a set of standard reference photographs used in the Optic Disc Reading Center of the Hamilton Glaucoma Center UCSD. This set of photographs included multiple examples of normal and definite glaucomatous optic discs. After training, each grader was certified after completing a test to evaluate his or her grading skills. For inclusion, photographs needed to be graded of adequate quality or better. The graders visually estimated the horizontal and vertical cup-disc ratios based on the contour of the cup.

Patients with OHT met the following criteria: baseline IOP greater than or equal to 24 mm Hg in one eye and greater than or equal to 21 mm Hg in the other eye, on at least 2 occasions; normal-appearing optic discs and retinal nerve fiber layer on baseline stereophotographs of both eyes (no diffuse or focal rim thinning, hemorrhage, cupping, or nerve fiber layer defects indicative of glaucoma or other ocular pathologic features); and normal visual field test results. Normal visual field test results were defined as a mean deviation and PSD within 95% confidence limits and a Glaucoma Hemifield Test result within normal limits.

FOLLOW-UP AND DETERMINATION OF PRIMARY OPEN-ANGLE GLAUCOMA END POINTS

Conversion from OHT to glaucoma was considered as the development of a reproducible visual field defect or glaucomatous change in the appearance of the optic disc in at least 1 eye. The time of the first abnormal SAP visual field test results or change in optic disc appearance (whichever came first) in the eye that developed primary open-angle glaucoma (POAG) was defined as the end point for patients showing conversion.

Glaucomatous change in the appearance of the optic disc was defined as the development of focal or diffuse thinning of the neuroretinal rim, increased excavation, or appearance of retinal nerve fiber layer defects. Changes in rim color, presence of disc hemorrhage, or progressive parapapillary atrophy were not sufficient for characterization of progression. When grading photographs for progression, each examiner was masked to the temporal sequence of the photographs. Discrepancies between the 2 graders were either resolved by consensus or by adjudication of a third experienced grader.

Abnormality on SAP was defined as the presence of a Glaucoma Hemifield Test result outside normal limits and/or PSD with $P<.05$. Based on previous results from the OHTS, a confirmed visual field defect required 3 consecutive, abnormal visual field test results.[6] The visual field test results were also evaluated by a glaucoma specialist who excluded other causes of nonglaucomatous visual field loss or presence of visual field artifacts as possible causes of the visual field abnormality. Only reliable visual field test results were included in the analysis. This was defined as 33% or fewer false-positive results, false-negative results, and fixation losses. One hundred ninety-five (5.6%) of 3509 visual field test results were classified as unreliable and excluded from the analysis.

None of the patients were receiving any ocular hypotensive medication at baseline, and they also were left untreated during follow-up. Fifteen (12%) of the 126 patients were assigned to treatment during follow-up for other causes than development of glaucoma, such as unacceptably high IOP (based on the attending ophthalmologist's decision). For these patients, only the period without treatment was evaluated in the study. No evidence for informative censoring was found when the analyses were repeated after exclusion of these patients or after assigning them to the conversion group. Therefore, we report only the results of the analyses considering these patients as censored when they first received treatment.

DATA ANALYSIS

For eye-specific variables, we calculated the mean for each eye and then averaged the mean values from each eye to determine the baseline predictive factor for each participant. We chose to average the 2 eyes to replicate OHTS methods.[2] The IOP predictive factor was calculated from 2 to 4 baseline IOP measurements per eye obtained during the first 6 months of follow-up.

DEVELOPMENT OF PREDICTIVE MODELS

The OHTS was a large prospective study evaluating the risk for conversion from OHT to glaucoma. The study randomized 1636 patients with OHT for treatment or observation and demonstrated that medication prevents or delays the onset of POAG. In addition, the OHTS investigators evaluated several potential baseline risk factors to determine their association with the risk of glaucoma development during follow-up.[2] The OHTS multivariate analysis (using Cox proportional hazards models) identified 6 factors as being significantly associated with the risk for development of POAG during follow-up: age, diabetes mellitus, baseline IOP, CCT, vertical cup-disc ratio, and PSD. Horizontal cup-disc ratio was also significantly associated with glaucoma development in multivariate analysis; however, because of its high correlation with vertical cup-disc ratio and slightly better predictive power of the latter, only vertical cup-disc ratio was included in the final multivariate model.[2]

Based on published OHTS results, we developed predictive models for the 5-year risk of conversion from OHT to glaucoma for untreated patients. The following formula can be used to estimate individual risk using the Cox regression model[7]:

$$\text{Risk estimate} = 1 - S_0(t)^{\exp\left(\sum_{i=1}^{k}\beta_i X_i - \sum_{i=1}^{k}\beta_i \bar{x}_i\right)},$$

where $S_0(t)$ is the average survival at time t (eg, $t=5$ years) or the survival rate at the mean values of the risk factors, βs are the Cox regression coefficients, Xs are the individual's values on the k risk factors, and $\bar{x}$s are the means of the risk factors. The linear parameter:

$$\sum_{i=1}^{k}\beta_i X_i - \sum_{i=1}^{k}\beta_i \bar{x}_i$$

is often referred to as the prognostic index (PI) and is calculated for each individual patient.[8]

Two risk models were developed from the OHTS results, one including all 6 predictor variables identified by the multivariate analysis (full model) and the other using all variables but excluding vertical cup-disc ratio and PSD (reduced model). This latter model was developed to avoid the inclusion in the predictive model of variables involved in the definition of the outcome.[9]

The following general formula can be used to estimate the risk of glaucoma development in 5 years for an individual untreated patient with OHT using the Cox proportional hazards regression model[7]:

$$\text{Risk estimate} = 1 - S_0(t)^{\exp(PI)}; \text{ where } PI = \sum_{i=1}^{k}\beta_i X_i - \sum_{i=1}^{k}\beta_i \bar{x}_i,$$

where $S_0(t)$ is the survival rate at the mean values of the risk factors obtained from the estimated baseline survivorship function. Because the baseline survivorship function was not explicitly provided in the OHTS results, we have approximated by the average survival probability at 5 years obtained from OHTS Kaplan-Meier estimates. To calculate *PI*, the coefficients (βs) of the risk factors are calculated by obtaining the natural logarithm (ln) of the hazard ratios published in the OHTS, taking into account the reference units. Xs are the individual's values of the risk factors and $\bar{x}$'s are the mean values of the risk factors from the OHTS cohort. Data on the average survival time, Cox regression coefficients, and means of risk factors were obtained from the OHTS publications.[1,2,9-11]

For the full OHTS-derived risk model (containing all 6 predictor variables), the risk estimate for glaucoma development in 5 years can be calculated as:

risk estimate = $1 - 0.906^{\exp(PI)}$,

where $PI = (\ln(1.25)/10) \times \text{age} + \ln(1.11) \times \text{IOP} + (\ln(1.25)/0.2) \times \text{PSD} - (\ln(1.82)/40) \times \text{CCT} + (\ln(1.32)/0.1) \times (\text{vertical cup-disc ratio}) + \ln(0.35) \times (\text{diabetes mellitus}) - (\ln(1.25)/10) \times 55.4 - \ln(1.11) \times 24.9 - (\ln(1.25)/0.2) \times 1.90 + (\ln(1.82)/40) \times 574.5 - (\ln(1.32)/0.1) \times 0.39 - \ln(0.35) \times 0.121$.

The variable "diabetes mellitus" receives 1 if the patient has a history of diabetes mellitus and 0 otherwise. For example, using the full model, the risk of glaucoma development in 5 years for a 60-year-old patient without diabetes mellitus with untreated OHT and a baseline IOP of 26 mm Hg, CCT of 570 µm, vertical cup-disc ratio of 0.4, and PSD of 1.9 is:

$PI = (\ln(1.25)/10) \times 60 + \ln(1.11) \times 26 + (\ln(1.25)/0.2) \times 1.9 - (\ln(1.82)/40) \times 570 + (\ln(1.32)/0.1) \times 0.4 + \ln(0.35) \times 0 - (\ln(1.25)/10) \times 55.4 - \ln(1.11) \times 24.9 - (\ln(1.25)/0.2) \times 1.90 + (\ln(1.82)/40) \times 574.5 - (\ln(1.32)/0.1) \times 0.39 - \ln(0.35) \times 0.121 = 0.4396$.

The risk estimate is then calculated by:

risk estimate = $1 - 0.906^{\exp(PI)} = 1 - 0.906^{\exp(0.4396)} = 0.1420$.

Therefore, the risk estimate for glaucoma development in 5 years for this patient is approximately 14%.

For the reduced model, excluding vertical cup-disc ratio and PSD, the risk estimate is calculated as follows:

risk estimate = $1 - 0.906^{\exp(PI)}$,

where $PI = (\ln(1.29)/10) \times \text{age} + \ln(1.10) \times \text{IOP} - (\ln(1.92)/40) \times \text{CCT} + \ln(0.38) \times (\text{diabetes mellitus}) - (\ln(1.29)/10) \times 55.4 - \ln(1.10) \times 24.9 + (\ln(1.92)/40) \times 574.5 - \ln(0.38) \times 0.121$.

For example, using the reduced model, the risk estimate of glaucoma development in 5 years for a 60-year-old patient without diabetes mellitus and with untreated OHT and a baseline IOP of 26 mm Hg and CCT of 570 µm is:

$PI = (\ln(1.29)/10) \times 60 + \ln(1.10) \times 26 - (\ln(1.92)/40) \times 570 + \ln(0.38) \times 0 - (\ln(1.29)/10) \times 55.4 - \ln(1.10) \times 24.9 + (\ln(1.92)/40) \times 574.5 - \ln(0.38) \times 0.121 = 0.41244$.

The risk estimate is then calculated by:

risk estimate = $1 - 0.906^{\exp(PI)} = 1 - 0.906^{\exp(0.41244)} = 0.1385$.

Therefore, the risk estimate for glaucoma development in 5 years for this patient is approximately 14%.

Although the earlier equations can be used to estimate the risk for a given subject, the calculations can be tedious. To simplify the calculations, we also present a scoring system,

where integer points are assigned to each level of each risk factor so that the clinician can easily approximate

$$\sum_{i=1}^{k} \beta_i X_i$$

for a specific risk factor profile by summing integer points.[12,13] In brief, points were assigned to each risk factor according to the product of the corresponding β coefficient and the value of the risk factor. Fractional values were converted to integer values by dividing by a constant. For each possible score, a linear function was computed and corrected for the means of the risk factors in the OHTS cohort. The results were inserted into a survival function (as shown earlier) to estimate the risk. A points system was developed to predict the risk for conversion from OHT to glaucoma in 5 years, and its results were compared with risk estimates obtained using the Cox regression equation directly.

VALIDATION OF THE PREDICTIVE MODELS

The main purpose of this study was to validate the predictive models developed from OHTS results on an independent population. The performance of the OHTS predictive models was assessed in the DIGS cohort according to 3 evaluations: equality of regression coefficients (hazard ratio comparison), discrimination, and calibration.[14]

As a first step, we tested whether the regression coefficients of the OHTS predictive models were similar to the coefficients obtained when the model was developed using the DIGS population. For this purpose, Cox proportional hazards regression functions were derived using the same variables identified as predictive in the OHTS but using only data from the DIGS cohort. Two predictive models were derived, one using all 6 variables previously described (age, diabetes mellitus, IOP, CCT, vertical cup-disc ratio, and PSD) and the other using these variables but excluding vertical cup-disc ratio and PSD. These models were called DIGS predictive models, and they represent the best possible Cox predictive functions using these variables according to the prevalence of the evaluated risk factors on the DIGS cohort. For each risk factor, the regression coefficients for the OHTS- and DIGS-derived models were compared using a z statistic where $z=(b_{[OHTS]}-b_{[DIGS]})/SE$, where $b_{[OHTS]}$ and $b_{[DIGS]}$ are the regression coefficients for the OHTS- and DIGS-derived models, respectively. SE is the standard error of the difference in the coefficients where

$$SE = \sqrt{SE^2_{[OHTS]} + SE^2_{[DIGS]}}.$$

Because the hazard ratio of a risk factor is an exponential function of its regression coefficient, the z statistic can be used to assess differences in hazard ratios between the 2 functions. To make it more likely to find a difference if one exists between the OHTS- and DIGS-derived coefficients, $P<.10$ was defined as significant.[15,16] To further evaluate whether hazard ratios were correctly specified in the OHTS-derived models in relation to the DIGS population, Cox proportional hazards regression models were fitted in the DIGS data set using the PI as a single covariate. If the regression coefficient β equals 1, the relative risk model is valid; if β does not equal 1, there is a need for calibration.[8]

In our application, discrimination is the ability of a predictive model to separate those patients with OHT who develop glaucoma from those who do not (ie, it is an estimate of the probability that the model assigns a higher risk for those who develop glaucoma than those who do not). For each predictive model, discrimination was assessed by calculating the *c*-index as proposed by Harrell et al,[14] which is analogous to the area under the receiver operating characteristic curve.[17] The *c*-index is calculated as the proportion of all usable subject pairs in which the predictions and outcomes are concordant. If the predicted survival time is larger for the subject who actually survived longer, the predictions of the pair are concordant with the outcomes. In predicting the time to an event, *c* is calculated using all possible pairs of subjects, at least one of whom has had the event occur (in our application, conversion to glaucoma). Two subjects' survival times cannot be ordered if both subjects are censored or if one has failed and the follow-up time of the other is less than the failure time of the first.[18] A *c* value of 0.5 indicates random predictions, whereas a value of 1.0 indicates perfect prediction. To test for the significance of the difference in discrimination between 2 models, we used the *rcorrp.cens* function from the Harrell Hmisc/Design library.[19] This computes *U* statistics for testing whether the predictions of one model are more concordant with actual observations than those of another model. A *P* value less than .05 was considered statistically significant.

Calibration measures how closely predicted outcomes agree with actual outcomes. To assess calibration, the predictive risks calculated for the DIGS population using the OHTS-derived models were used to divide subjects into quartiles of predicted risk for developing glaucoma in 5 years. In each of the quartiles, the average predicted risk at 5 years was compared with the average outcome at 5 years, as obtained from Kaplan-Meier survival estimates.[18]

Statistical analyses were performed using software S-PLUS version 6.0 (Insightful Corporation, Seattle, Wash) and SPSS version 13.0 (SPSS Inc, Chicago, Ill).

RESULTS

Baseline demographic and clinical characteristics of the 126 patients with OHT included in the current study (DIGS) and the 819 participants with OHT in the untreated arm of OHTS are presented in **Table 1**. With the exception of a smaller proportion of African American participants in DIGS, the demographic and clinical characteristics of participants in the 2 studies were similar. Average follow-up time was 86 months (median, 76 months; range, 14-198 months). Thirty-one subjects (25%) developed POAG during follow-up. **Table 2** presents baseline characteristics of the DIGS patients who developed and did not develop glaucoma. Seventeen (55%) of the converters reached the end point based on development of optic disc changes, 10 (32%) based on progressive visual field loss, and 4 (13%) based on concurrent optic disc and visual field changes. **Figure 1** shows the observed cumulative probability of developing glaucoma during follow-up. The average probability of glaucoma conversion at 5 years was 11.6%.

COMPARISON OF HAZARD RATIOS

Table 3 presents the hazard ratios from the Cox regression models obtained in the DIGS population and hazard ratios reported by the OHTS.[9] For the models containing all 6 predictor variables, hazard ratios from DIGS- and OHTS-derived models were similar for age ($P=.37$), IOP ($P=.42$), CCT ($P=.82$), vertical cup-disc ratio ($P=.21$), and PSD ($P=.61$). Using $\alpha=.10$ as a sig-

nificance level, hazard ratios were significantly different for diabetes mellitus ($P=.08$). For the models excluding vertical cup-disc ratio and PSD, hazard ratios from DIGS- and OHTS-derived models were similar for age ($P=.31$), IOP ($P=.40$), and CCT ($P=.69$) but were significantly different for diabetes mellitus ($P=.06$).

To further assess whether hazard ratios were correctly specified in the OHTS-derived models in relation to the DIGS population, we fitted Cox proportional hazards models in the DIGS data set using the PI as a single covariate. This resulted in a coefficient of 0.826 (SE=0.195) for the OHTS-derived model containing all

Table 1. Baseline Demographic and Clinical Factors for Patients With Ocular Hypertension Included in the Current Study (DIGS) and in the Observation Group of the OHTS*

Factor	DIGS (n = 126)	OHTS (n = 819)
Age, y, mean ± SD	56.3 ± 13.1	55.4 ± 9.6
Race, No. (%)		
White, non-Hispanic	118 (94)	560 (68)
African American	4 (3)	205 (25)
Hispanic	2 (2)	35 (4)
Asian	2 (2)	10 (1)
Other	0	9 (1)
Female, %	58	58
Diabetes mellitus, No. (%)	14 (11)	99 (12)
IOP, mm Hg, mean ± SD	25.7 ± 3.5	24.9 ± 2.7
CCT, µm, mean ± SD	576.8 ± 36.7	574.5 ± 37.7†
Vertical cup-disc ratio, mean ± SD	0.43 ± 0.15	0.39 ± 0.19
Horizontal cup-disc ratio, mean ± SD	0.43 ± 0.15	0.36 ± 0.18
PSD, dB, mean ± SD	1.78 ± 0.36	1.90 ± 0.21

Abbreviations: CCT, central corneal thickness; DIGS, Diagnostic Innovations in Glaucoma Study; IOP, intraocular pressure; OHTS, Ocular Hypertension Treatment Study; PSD, pattern standard deviation.

*Data on baseline factors of OHTS subjects were obtained from Kass et al[1] and Gordon and Kass.[11]

†For CCT, n = 699 for the observation group in the OHTS.

Table 2. Baseline Demographic and Clinical Factors for Patients With Ocular Hypertension From the DIGS Population Who Developed and Did Not Develop Glaucoma

Factor	Developed Glaucoma (n = 31)	Did Not Develop Glaucoma (n = 95)
Age, y, mean ± SD	59.5 ± 11.3	55.2 ± 13.6
Race, No. (%)		
White, non-Hispanic	29 (94)	89 (94)
African American	2 (6)	2 (2)
Hispanic	0	2 (2)
Asian	0	2 (2)
Female, %	52	60
Diabetes mellitus, No. (%)	5 (16)	9 (10)
IOP, mm Hg, mean ± SD	26.7 ± 3.0	25.4 ± 3.6
CCT, µm, mean ± SD	559.8 ± 38.7	582.4 ± 34.4
Vertical cup-disc ratio, mean ± SD	0.42 ± 0.15	0.43 ± 0.16
Horizontal cup-disc ratio, mean ± SD	0.39 ± 0.13	0.43 ± 0.15
PSD, dB, mean ± SD	1.96 ± 0.44	1.72 ± 0.32

Abbreviations: CCT, central corneal thickness; DIGS, Diagnostic Innovations in Glaucoma Study; IOP, intraocular pressure; PSD, pattern standard deviation.

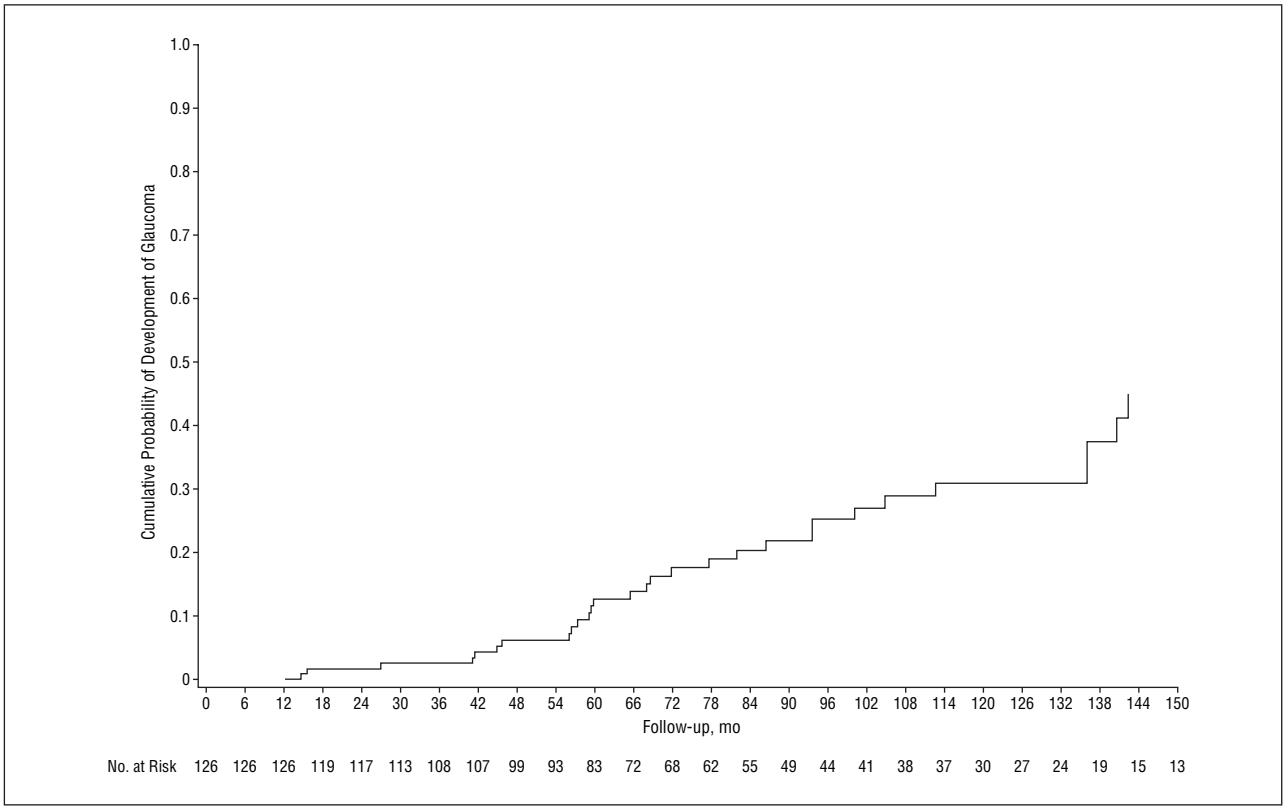

Figure 1. Kaplan-Meier plot of the cumulative probability of glaucoma development during follow-up.

Table 3. Hazard Ratios With 95% Confidence Intervals for Risk Factors Associated With Development of Glaucoma*

	OHTS		DIGS	
Factor	Full Model	Reduced Model	Full Model	Reduced Model
Age (per decade older)	1.25 (1.04-1.49)	1.29 (1.09-1.53)	1.49 (1.06-2.11)	1.56 (1.13-2.16)
IOP (per mm Hg higher)	1.11 (1.05-1.18)	1.10 (1.04-1.17)	1.17 (1.05-1.30)	1.16 (1.04-1.29)
CCT (per 40-µm thinner)	1.82 (1.51-2.19)	1.92 (1.60-2.30)	1.92 (1.25-2.96)	2.10 (1.39-3.18)
Diabetes mellitus	0.35 (0.15-0.78)	0.38 (0.17-0.86)	1.13 (0.40-3.18)†	1.28 (0.47-3.46)†
Vertical cup-disc ratio (per 0.1 larger)	1.32 (1.20-1.45)	Excluded	1.10 (0.85-1.44)	Excluded
PSD (per 0.2-dB higher)	1.25 (1.06-1.48)	Excluded	1.15 (0.95-1.39)	Excluded

Abbreviations: CCT, central corneal thickness; DIGS, Diagnostic Innovations in Glaucoma Study; IOP, intraocular pressure; OHTS, Ocular Hypertension Treatment Study; PSD, pattern standard deviation.

*Values are expressed as hazard ratio (95% confidence interval). Full model contains all 6 predictor variables; reduced model excludes vertical cup-disc ratio and PSD.

†Difference between the DIGS-derived model and OHTS-derived model was statistically significant (with $\alpha = .10$).

6 variables and 1.086 (SE=0.255) for the OHTS-derived model excluding vertical cup-disc ratio and PSD. The coefficients for both models were not significantly different than 1.0 ($P>.10$ for both analyses).

DISCRIMINATION

When applied to the DIGS cohort, the full and reduced OHTS predictive models had *c*-indexes of 0.68 and 0.73, respectively. There was no statistically significant difference in discrimination between the 2 models ($P=.07$).

When DIGS-derived models were applied to the DIGS population, discrimination was similar to that of the OHTS-derived models, with a *c*-index of 0.75 for the model containing all 6 variables and 0.74 for the model without vertical cup-disc ratio and PSD. Discrimination estimates for the DIGS-derived models are overestimated because they are based on the same cohort from which the models were developed.

CALIBRATION

When applied to the DIGS population, the average of the predicted probabilities for glaucoma conversion in 5 years was 14.3% for the full OHTS-derived model and 12.6% for the reduced OHTS-derived model. The average probabilities calculated by the OHTS-derived predictive models were similar to the observed average probability for glaucoma conversion in 5 years (11.6%) obtained from the Kaplan-Meier curve.

Figure 2 shows calibration plots with predicted vs observed probabilities of glaucoma conversion in 5 years for both OHTS-derived models when applied to the DIGS patients. In general, there was good agreement between predicted and observed probabilities. The full OHTS-derived model tended to overestimate probabilities in the highest-risk quartile, with a difference of 7% between predicted and observed probabilities (Figure 2A), whereas the reduced OHTS-derived model tended to underestimate probabilities in the highest-risk quartile, with a difference of 6.5% between predicted and observed probabilities (Figure 2B).

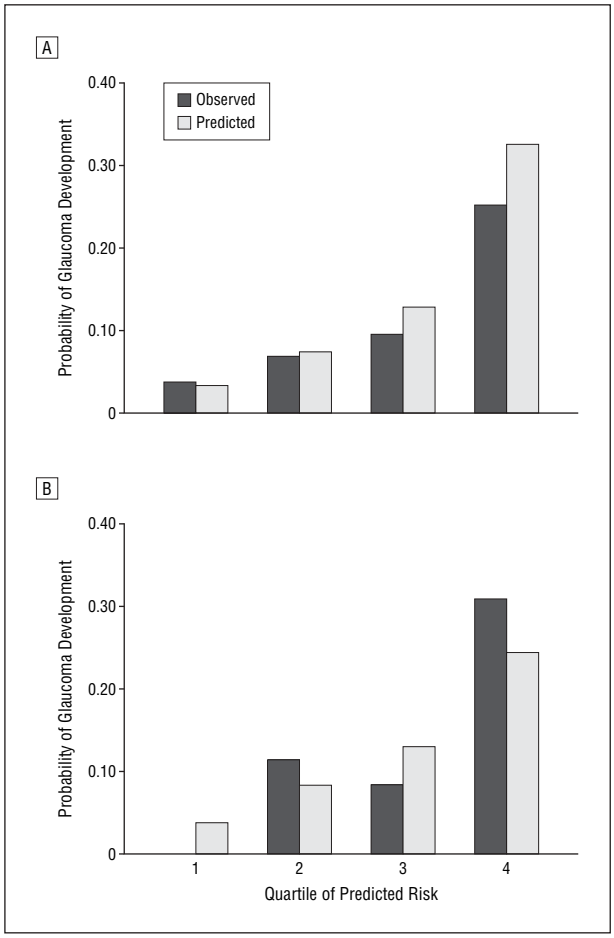

Figure 2. Calibration plots of the 5-year prediction of glaucoma development according to the OHTS-derived full (A) and reduced (B) models. The x-axis refers to the quartile of predicted risk based on the OHTS-derived models. Average predicted probabilities within each quartile are compared with observed probabilities obtained by Kaplan-Meier estimates for each quartile.

RISK SCORING SYSTEM

A points system was developed to estimate the risk of development of glaucoma in 5 years (**Figure 3**). Because the 2 OHTS-derived predictive models had similar per-

Step 1

Age, y	Points
40-44	0
45-49	1
50-54	2
55-59	3
60-64	4
65-69	5
70-74	6
75-80	7

Step 2

IOP, mm Hg	Points
23	0
24	1
25	2
26	3
27	4
28	5
29	6
30	7
31	7
32	8

Step 3

CCT, µm	Points
450-469	30
470-489	27
490-509	24
510-529	21
530-549	19
550-569	16
570-589	13
590-609	11
610-629	8
630-649	5
650-669	3
670-689	0

Step 4

Vertical Cup-Disc Ratio	Points
0.1	0
0.2	2
0.3	5
0.4	7
0.5	10
0.6	12
0.7	15
0.8	17
0.9	20

Step 5

PSD	Points
1.00-1.19	0
1.20-1.39	2
1.40-1.59	4
1.60-1.79	6
1.80-1.99	8
2.00-2.19	10
2.20-2.39	12
2.40-2.59	14

Step 6

Diabetes Mellitus	Points
Yes	–9
No	0

Step 7

Add Up Points From Steps 1 Through 6

Look Up Below the Predicted 5 to Year Risk of Glaucoma Development

Total Points	5-Year Risk, %
–9 to 12	<1
13 to 27	1 to 5
28 to 33	6 to 10
34 to 37	11 to 15
38 to 40	16 to 20
41 to 44	21 to 30
45 to 47	31 to 40
48 to 50	41 to 50
>50	>50

Figure 3. Scoring system for estimation of the 5-year risk of glaucoma development for untreated patients with ocular hypertension. To calculate the predicted risk for an individual patient, the scores for each risk factor are calculated on steps 1 through 6 and then summed to give a total score, which is converted to a predicted risk for glaucoma development in 5 years (step 7). CCT indicates central corneal thickness; IOP, intraocular pressure; PSD, pattern standard deviation.

formances, the points system was developed only for the more general, full OHTS-derived predictive model.

To calculate the predicted risk for an individual patient, the scores for each risk factor are summed and the total score is then converted to a predicted risk for glaucoma development in 5 years according to the 7 steps presented in Figure 3. For instance, a 60-year-old patient without diabetes mellitus and with a baseline IOP of 26 mm Hg, CCT of 570 µm, vertical cup-disc ratio of 0.4, and PSD of 1.9 receives a score of 35 points for predicting glaucoma: 4 points for age (step 1), 3 points for IOP (step 2), 13 points for CCT (step 3), 7 points for vertical cup-disc ratio (step 4), 8 points for PSD (step 5), and no points for absence of diabetes mellitus (step 6). This score corresponds to a predicted 5-year risk of glaucoma conversion between 11% and 15% (step 7).

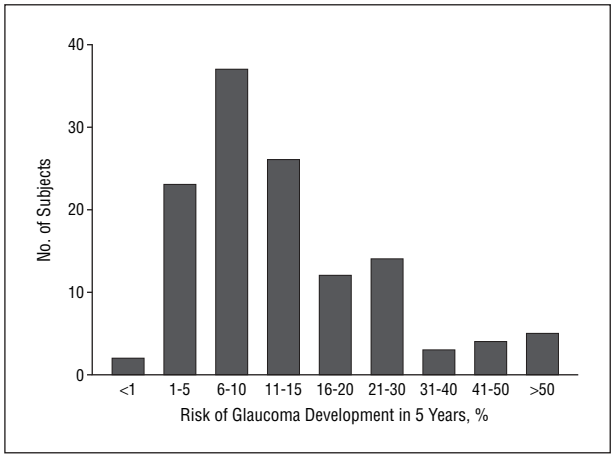

Figure 4. Distribution of predicted probabilities for the 5-year risk of glaucoma development among the 126 untreated patients with ocular hypertension included in the study.

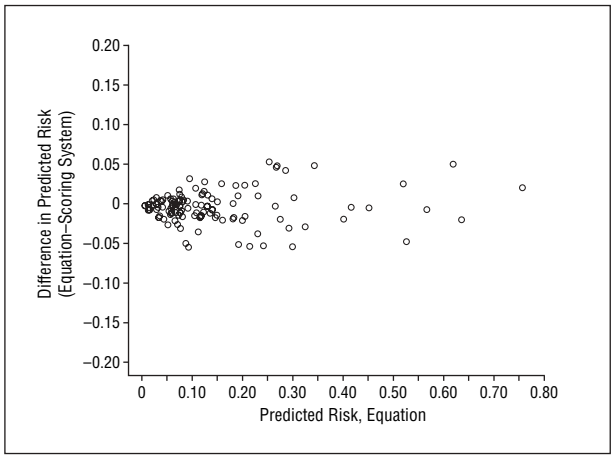

Figure 5. Scatterplot of the differences between risk estimates obtained by the scoring system and by direct application of the Cox regression equation.

Using the risk scoring system presented in Figure 3, predicted probabilities for glaucoma conversion were calculated for each patient with OHT from the DIGS cohort. The percentage of patients in each of the arbitrary risk categories is presented in **Figure 4**. There was almost perfect agreement between predicted risks as estimated from the points system and those estimated directly from the Cox regression equations for these arbitrary risk categories (weighted κ coefficient=0.97). **Figure 5** shows a scatterplot of the differences between the predicted risks using the points system and predicted risks estimated directly from the Cox regression equation. The differences were within 3% for 111 patients (88%) and within 5% for all patients.

COMMENT

In the current study, we developed predictive functions for the risk of glaucoma development in 5 years for untreated subjects with OHT. Evaluation of relative risks, discrimination, and calibration in an independent population suggested that these models generalize well for prediction of the risk of glaucoma

conversion in an independent population of patients with OHT.

The relative risks for the predictive factors for glaucoma development previously identified by the OHTS were similar to those found in our independent population of patients with OHT. Older age, higher baseline IOP, and thinner corneas were all significantly associated with an increased risk of glaucoma development in the DIGS population, also confirming the results of several other publications.[20-23] Relative risks for baseline vertical cup-disc ratio and PSD were also similar to those reported by the OHTS, although their association with glaucoma development was smaller in our population. Contrary to the OHTS results, however, a history of diabetes mellitus was not a significantly protective factor in our population. This may be because of the relatively small number of end points (conversions) in our study, resulting in large confidence intervals and insufficient power to detect a significant association. In fact, even in the OHTS, a multicenter effort involving more than 1600 patients and 148 end points, reported confidence intervals for the association of diabetes mellitus with risk of glaucoma conversion among patients with OHT were relatively large.[2,9] In both studies, diagnosis of diabetes mellitus was based on self-reported history, but no confirmatory blood tests were performed. Also, patients with diabetic retinopathy were excluded from both studies, which may have resulted in the evaluation of an unrepresentative group of patients with diabetes mellitus. In the present study, we did not attempt to revise the OHTS-derived predictive models by changing the coefficients of the covariates because this would require a third population to validate the revised model. Further, considering the limitations of the included populations, the OHTS still represents the best available evidence for the importance of diabetes mellitus as a risk factor for development of glaucoma.

The ability of the OHTS-derived predictive models to discriminate subjects who developed glaucoma from those who did not was reasonably good with *c*-indexes of 0.68 and 0.73 for the full and reduced models, respectively. A *c*-index of 0.73 indicates that in 73% of the cases the model allocated a higher predicted probability for a subject who actually developed glaucoma than for a subject who did not. These values are similar to those found when risk models such as the Framingham coronary prediction scores are used to predict coronary heart disease events.[15,16] D'Agostino et al[16] reported *c*-indexes ranging from 0.63 to 0.83 when the Framingham functions were applied to 6 different cohorts of patients.

Besides discrimination, an important question to decide whether a model is valid is: "Are the predictions of the model reliable?" To answer this question, the predicted probabilities as calculated with the model need to be compared with the observed probabilities. A reliable or well-calibrated model will give predicted probabilities that agree numerically with the actual outcomes. The average predicted probabilities of glaucoma development obtained from the OHTS-derived models (14.3% and 12.6% for the full and reduced models, respectively) were similar to the actual probability of glaucoma conversion found in the DIGS cohort (11.6%). After stratifying the patients in quartiles according to predicted risk categories, a good agreement was also observed in the different groups.

In the present study, the full model containing vertical cup-disc ratio and PSD performed similarly to the reduced model that excluded these variables. Although vertical cup-disc ratio and PSD may be indicators of glaucomatous damage rather than risk factors for development of the disease, their incorporation into the predictive model may help clinicians identify patients at an early stage of the disease. Therefore, because estimates of vertical cup-disc ratio and PSD can be easily obtained, we believe that the more general model, which incorporates these variables, is likely to be more helpful in clinical practice. Vertical cup-disc ratio estimates in the OHTS and DIGS were obtained from evaluation of optic disc stereophotographs by masked, experienced observers, which can be different from estimates obtained during ophthalmoscopic examination. Moreover, estimates of vertical cup-disc ratio can sometimes differ largely among different examiners.[24,25]

Because multivariate models are fairly complex, we developed a points system to simplify the calculations of risk estimates. The points system, as presented in Figure 3, can provide an easy way for clinicians to estimate the risk of glaucoma development for an individual patient, using simple arithmetic that can be applied without a calculator or computer. Scoring systems similar to the one proposed in our study have been widely used to estimate the risk of cardiovascular events.[12] The final points system presented in our study was developed based only on the full OHTS-derived predictive model, for the reasons described in the previous paragraph. Therefore, to estimate the risk for an individual patient with OHT, the clinician will need the information on the 6 predictive factors: age, IOP, CCT, vertical cup-disc ratio, PSD, and presence or absence of diabetes mellitus. After collecting this information, the score sheet can be used to estimate the risk of glaucoma conversion at 5 years for an untreated subject following the 7 steps as detailed in Figure 3. This scoring system should not be used to evaluate risk in treated patients or to reassess risk after the patient has started treatment.

How can we evaluate the clinical usefulness of a predictive model if this model is to be incorporated into clinical practice? To evaluate this, a clinically relevant threshold value needs to be established (ie, the risk above which the expected benefits of treatment outweigh the possible risks).[26,27] To exemplify calculations of clinical usefulness, let's assume a hypothetical threshold of 15% for treatment[3] (ie, all patients with OHT with risk estimates for glaucoma development in 5 years more than 15% [or a score higher than 37 using the points system of Figure 3] would be treated). A threshold value of 15% implies that leaving untreated a patient who later develops glaucoma is approximately 5.5 (0.85 divided by 0.15) times worse than treating a patient who does not develop the disease.[28] For the subjects with OHT included in our study, a threshold of 15% would imply treating 38 (30%) of the patients and leaving 88 (70%) untreated. Among the 88 patients with a predicted risk of 15% or lower, the actual risk of glaucoma development in 5 years, as estimated from Kaplan-Meier curves, was only 6%. Only 5

patients developed glaucoma in this group. On the other hand, among the 38 patients with a predicted risk higher than 15%, the actual risk of glaucoma development in 5 years was 26% (ie, 10 patients developed glaucoma in this group). The clinical usefulness of a predictive model could be quantified as the relative reduction in the number of unnecessarily treated patients.[29] For the DIGS cohort, a reference policy of treating all patients would result in 111 patients (88%) being unnecessarily treated. Using the risk model, the number of patients unnecessarily treated would be reduced to 28 (22%), although at the expense of leaving untreated 5 patients who later would develop glaucoma. If the ratio of 5.5 is used to weight false classifications, the relative reduction in unnecessarily treated patients would be $(111 - [28 + 5.5 \times 5])/111 = 50\%$. Therefore, compared with a reference policy of treating all patients, the application of the risk model would result in better targeting of treatment for patients with a higher risk of developing glaucoma. This may be especially important in light of the evidence provided by the OHTS that 40% of treated patients required 2 medications and 10% required 3 medications to achieve a 20% reduction of IOP, indicating that substantial costs may be involved in preventing 1 patient with OHT from developing glaucoma.

In this study, we have estimated predictive models for the risk of glaucoma development for patients with OHT left untreated during follow-up. We did not attempt to develop functions for estimating the risk of glaucoma development for patients with OHT undergoing treatment because the effect of treatment in preventing disease progression depends on several variables such as effectiveness, compliance, and persistence, which are very difficult to predict. By reporting the risk of an untreated patient for developing glaucoma, we wished to provide a tool for assessment of the risk of glaucoma development if the natural history of OHT is followed. This predictive model could be helpful for clinicians in deciding whether the magnitude of risk justifies treatment. However, along with risk assessment for glaucoma development, other factors, such as the patient's overall health status, life expectancy, and commitment to treatment, should be weighted against potentially adverse events and costs of treatment to provide an effective management of OHT.

To develop the predictive models in this study, we used the coefficients (hazard ratios) from the multivariate analyses reported in a previous OHTS publication.[9] These coefficients were reported for pooled treated and untreated subjects in the OHTS publications and no separate analysis was provided for the untreated group. As stated in the original OHTS article, "both analyses identified similar predictive factors"[2(p715)]; therefore, results were reported from models based on the entire sample. It is possible that model development using coefficients obtained only from the analysis of the subgroup under observation from the OHTS may produce a better model to estimate the risk for untreated subjects. The prediction models developed in our study incorporated only baseline variables, as measured at the beginning of follow-up. This implies that these values do not change over time or that the initial measurements are the most relevant for risk prediction. This may be a valid assumption for a short-term risk assessment, and the results of our validation study corroborate with this. However, some risk factors may show considerable intraindividual changes over time so that the correlation between their baseline and updated values gradually decreases with follow-up.[30] In fact, IOP fluctuations over long periods have been suggested to be an important risk factor for glaucoma progression,[31] and variations in IOP are likely to occur in a patient with OHT followed up over time. It is possible that models developed to incorporate updated risk factors over time would provide an improved risk assessment.[32,33] Development of these models, however, requires assessment of the optimal frequency of updating of risk factor measurements and other complex issues.[32]

In general, the direct application of predictive models may be the most appropriate for individuals who resemble the cohort from which the model was derived. Our inclusion and exclusion criteria were very similar to those used by the OHTS. In addition, the proportions of patients reaching each of the specific end points in the DIGS population (55%, optic disc; 32%, visual field; and 13%, concurrent optic disc and visual field) were very similar to those reported by the OHTS (57%, 33%, and 10%, respectively). In both studies, the majority of patients were of white origin. For populations with different ethnic backgrounds or different prevalence of risk factors, the adoption of established models can also be helpful; however, validation of their application must be evaluated before incorporation into local practice and guidelines.[15] Further, although the OHTS was the largest study to evaluate predictive factors for glaucoma development among subjects with OHT, it is possible that other variables that have not yet been identified may be related to the risk of glaucoma development in some patients. As more results from the OHTS investigations become available, such as those provided by the confocal scanning laser ophthalmoscopy and short-wavelength automated perimetry ancillary arms, it is likely that the predictive capabilities of the models will be enhanced by inclusion of other variables.[34]

In conclusion, our results suggest that an OHTS-derived predictive model can be useful to assess the risk of glaucoma development in untreated patients with OHT. Incorporation of such a risk model into clinical practice could provide a better assessment of the global risk for disease development in a particular patient and help in clinical decision making regarding treatment.

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