The Probability of Glaucoma From Ocular Hypertension Determined by Ophthalmologists in Comparison to a Risk Calculator

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Objective: To investigate the ability of ophthalmologists to estimate an individual's risk of converting from ocular hypertension to glaucoma, and to compare these estimates to a risk calculator.

Design: Cross-Sectional Survey.

Methods: Fifty-one ophthalmologists estimated the probability of developing glaucoma of 4 factitious patients with ocular hypertension, after a didactic review of the Ocular Hypertension Treatment Study (OHTS) results. We compared the physician estimates to the probability estimates of a risk calculator on the basis of the multivariate Cox proportional hazard model of the OHTS results.

Results: The average estimates given by the ophthalmologists (mean probability ± SD) of developing glaucoma in 5 years for patient no. 1, patient no. 2, patient no. 3, and patient no. 4 were 6.5% ± 8.4 (range 1 to 50), 30.6% ± 20.5 (range 1 to 100), 7.1% ± 5.1 (range 0 to 20), and 21.1% ± 17.3 (range 1 to 80), respectively. The risk calculator estimated the probability of glaucoma in these same patients to be 13.7%, 53.8%, 5.1%, and 41.9%, respectively.

Conclusions: The ophthalmologists showed a high range of estimates for the probability of developing glaucoma in the same ocular hypertensive patients. This may lead to either under or over treatment of patients. Clinicians need a more exact method to determine the probability of glaucoma from ocular hypertension.

Key Words: ocular hypertension, glaucoma, risk calculator, randomized clinical trials, evidenced-based medicine

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Ocular hypertension is present in approximately 8% of adults over the age of 40 years in the United States.[1] Although ocular hypertension is a common finding, eye care providers do not know which patients to treat or which patients to monitor without treatment. Treating all ocular hypertensives is too expensive,[2] but avoiding treatment of all ocular hypertensive patients may needlessly increase the risk of glaucoma in susceptible patients. To address these issues, the Ocular Hypertension Treatment Study (OHTS) evaluated the safety and efficacy of ocular hypotensive medications for delaying or preventing the onset of primary open angle glaucoma in patients with ocular hypertension; and determined the baseline factors that predict the onset of primary open angle glaucoma in ocular hypertensive patients.[3,4]

The OHTS demonstrated that age, corneal thickness, intraocular pressure (IOP), pattern standard deviation (PSD), diabetes mellitus status, and vertical cup-to-disc ratio (C/D) were independent predictive variables for the development of glaucomatous optic disc or visual field changes. However, applying these findings to individual patients remains difficult because each patient encompasses a unique combination of risk factors that the clinician must take into account.[5] Even if one simplifies the risk assessment by dividing the continuous variables of age, corneal thickness, IOP, and PSD into thirds and uses 9 different combinations for C/D (0.0 to 0.8), 1458 ($3 \times 3 \times 3 \times 3 \times 2 \times 9$) different combinations of variables exist for ocular hypertension patients. This makes it difficult to determine the ocular hypertensive patients at highest risk for developing glaucoma.

The complexity of results from randomized controlled trials has created the need for risk calculators (or predictive models) in many fields of medicine. The most notable example is the Framingham Heart Study, which uses a scoring sheet to estimate the risk of cardiovascular disease with age, lipid levels, blood pressure, diabetes, and smoking history as explanatory variables.[6] We were interested if a similar need could be demonstrated in the management of ocular hypertension patients because of the complexity of results from OHTS.

We assessed the ability of a group of ophthalmologists to estimate the risk of developing glaucoma from ocular hypertension in comparison to a currently available risk calculator.[7] Although the goal of evidence-based

TABLE 1. Characteristics of Representative Ocular Hypertension Patients

	Patient no. 1	Patient no. 2	Patient no. 3	Patient no. 4
Diabetes Yes/No	**No**	**No**	**No**	**No**
Pattern Standard Deviation	1.9	1.9	1.9	1.9
Age (y)	60	72	60	60
IOP (mm Hg)	24	25	28	24
C/D	0.3	0.6	0.1	0.5
Corneal thickness (μm)	540	510	600	490

medicine is to apply results from well-designed, randomized controlled studies (such as OHTS) to the care of patients,[8] we hypothesized that it would be difficult for ophthalmologists to accurately apply the results to individual patients because of the complexity of findings in the OHTS.

METHODS

Legacy Health System Institutional Review Board (IRB) reviewed the study protocol and determined that the study is exempt from requiring IRB approval. We did not collect identifying information from the ophthalmologists; the ophthalmologists volunteered for the study; and the representative patients are fictional.

Written Survey

The authors presented the OHTS results[3,4] to ophthalmologists at 3 continuing medical education meetings occurring from October 2003 to February 2004. We used the OHTS study group slide set,[9] which included the rationale for the OHTS, the inclusion and exclusion criteria, and the baseline factors predictive of glaucoma including the univariate regression results, the multivariate regression results, and 2 cross table plots showing IOP versus corneal thickness and C/D versus corneal thickness. Each presentation included handouts with paper copies of the slides.

After presenting the results of the OHTS Study, the ophthalmologists in the audience completed a data collection form with their estimate of the probability of developing glaucoma over a 5-year period in 4 hypothetical ocular hypertension patients and whether or not they would treat each patient. They were able to use the handouts to guide their decisions. The presentation included the definition of glaucoma; which the OHTS defined as a reproducible visual field defect (confirmed twice) or reproducible clinically significant optic disc deterioration (confirmed once) that was attributable to glaucoma.[4]

Table 1 lists the characteristics of the 4 hypothetical ocular hypertension patients. The OHTS Study Group developed these patient scenarios to be illustrative of a typical ocular hypertensive patient. The OHTS patient profiles did not include PSD or diabetic status, so we added the same PSD of 1.9 (mean value of the OHTS patients) for each scenario and we stated that the patients did not have diabetes mellitus.

Our study compared the ophthalmologists' estimates to a risk calculator[7] developed from the results of the OHTS Study.[3,4] The risk calculator was derived from the OHTS multivariate Cox proportional hazard model by taking the natural log of the hazard ratios of the multivariate equation to create β coefficients for each covariate such as corneal thickness. The β coefficients are multiplied by the corresponding values of the covariates of a respective patient to determine a sum of the hazard model. The sum of an average OHTS participant is subtracted from the sum of the individual patient. Exponentiation of this difference with a base of 0.906 (overall survival of the OHTS patients) creates the likelihood of not developing glaucoma or probability of "survival." Subtracting this value from 1 creates the risk of developing glaucoma or the probability of "failure." The equation is shown below:

$$\text{Risk of Glaucoma} = 1 - 0.906^{\exp(\text{HFD})};$$

$$\text{where HFD} = \sum_{i=1}^{6} B_i X_i - \sum_{i=1}^{6} B_i X_{\text{mean}};$$

where HFD is the hazard function difference; 0.906 is the survival rate for the mean values of the OHTS; B_i is the β coefficients for the 6 covariates of the Cox proportional

TABLE 2. Ophthalmologist Estimates of the Probability (Risk) of Glaucoma in 5 y in the Representative Patients

	Patient no. 1	Patient no. 2	Patient no. 3	Patient no. 4
	n = 50	**n = 50**	**n = 49**	**n = 47**
Ophthalmologist estimates %				
Mean (25, 50, 75 percentile)	6.5 (2, 5, 5)	30.6 (18, 25, 40)	7.1 (3, 5, 10)	21.1 (10, 20, 25)
Median (Range)	5.0 (1-50)	25.0 (1-100)	5.0 (0-20)	20.0 (1-80)
Risk calculator estimate % (*P**)	13.7 (< 0.001)	53.8 (< 0.001)	5.1 (0.02)	41.9 (< 0.001)
OHTS Slide Set[9] Probability estimates % (*P**)	7 (0.001)	35 (0.04)	2 (< 0.001)	20 (= 0.73)

*As compared with the mean ophthalmologists' estimates (Wilcoxon Signed-Rank Test).

hazard model; X_i is the values of the risk factors for an individual patient; and X_{mean} is the values of the risk factors for the average OHTS participant.

Further details have been published previously.[7] In addition, we also compared the ophthalmologists' estimates to the probability estimate from the OHTS I Study Group slide set.[9]

Statistical Analysis

Statistical analysis was performed with SPSS (Version 10.0, Chicago, IL). We compared each ophthalmologist estimate to the risk estimate from the calculator. A P value less than or equal to 0.05 was considered statistically significant. We used a nonparametric test, the Wilcoxon Signed-Rank Test, to determine significance because the differences between the ophthalmologist probability estimates and the risk calculator were not normally distributed as shown by a Kolmogorov-Smirnov Test of Normality.[10]

RESULTS

We invited 60 ophthalmologists to participate and 51 (85%) ophthalmologists completed the data collection form. One ophthalmologist did not give a response for patient no. 1 and patient no. 2; 2 ophthalmologists did not give responses for patient no. 3; and 4 ophthalmologists did not give responses for patient no. 4. Therefore, sample sizes include 50 ophthalmologists for patients no. 1 and no. 2, 49 for patient no. 3, and 47 for patient no. 4.

Table 2 shows the ophthalmologists' estimated risk, the risk calculator estimate, and the OHTS slide set probability estimates. The ophthalmologists, on average, underestimated the risk of glaucoma in comparison to the risk calculator in patient no. 1, patient no. 2, and patient no. 4, but overestimated the risk in patient no. 3. A significant difference ($P < 0.05$) exists between the mean ophthalmologists' estimate in comparison to the estimate from the risk calculator for all 4 patients and when compared with the estimate from the OHTS slide set in 3 patients ($P < 0.05$). The estimates of the probability of developing glaucoma showed high variability, with a minimum range from 0% to 20% with patient no. 3 and a maximum range of 1% to 100% with patient no. 2 (Table 2).

Figures 1A to D show scatter plots and the distribution of responses for the 4 representative patients. They show a large variability in responses, and the different treatment decisions by individual ophthalmologists despite similar risk estimates. For example, Figure 1B shows a large variability of estimates with a range of estimates from 1% to 100%; and Figure 1C shows that even though an ophthalmologist's estimate was 10% for patient no. 3, he/she chose to treat, whereas another ophthalmologist did not treat even with a similar estimate.

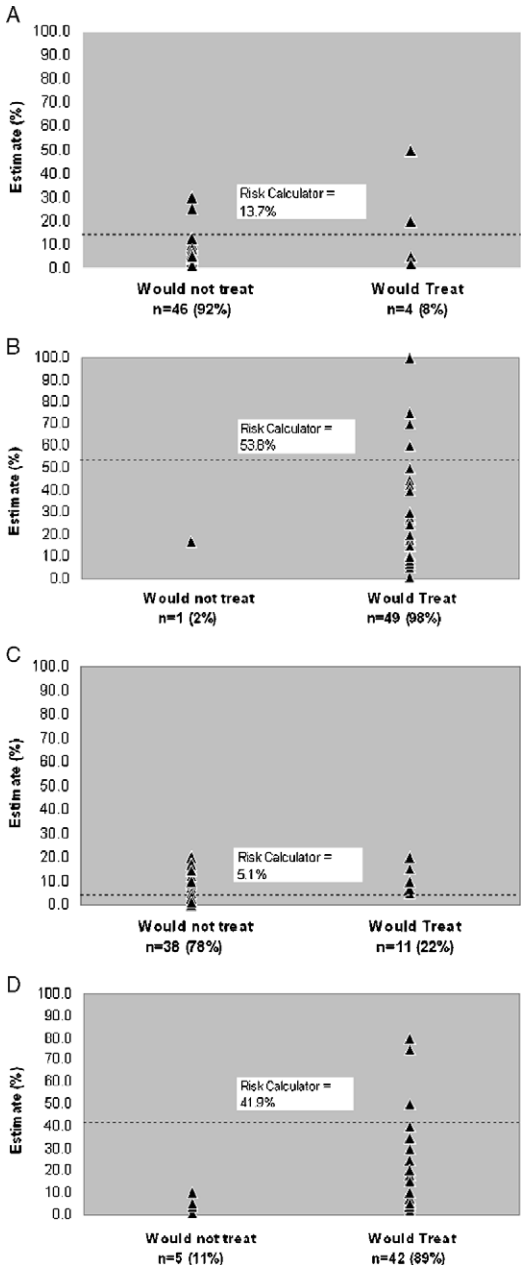

FIGURE 1. Scatterplots of ophthalmologists' estimate of risk (%) and whether or not they would treat. The dashed line within each figure represents the risk calculator estimate. A, Patient no. 1. B, Patient no. 2. C, Patient no. 3. D, Patient no. 4.

DISCUSSION

These results highlight the variability of ophthalmologists in estimating the probability of developing glaucoma in ocular hypertensive patients. Ophthalmologists were more likely to underestimate the risk of glaucoma, and whereas individual ophthalmologists may have similar estimations of risk, they differ in their decision to treat a given patient. Overall, these results

suggest that ophthalmologists may under or over treat the same ocular hypertensive patient due in part to the difficulty of interpreting the results of the OHTS study.

Benefits of a Risk Calculator

The OHTS multivariate regression contains 6 variables that are predictive of developing glaucoma from ocular hypertension: age, corneal thickness, IOP, PSD, diabetes status, and vertical C/D. As stated previously, this creates a large number of different combinations of variables for any 1 ocular hypertension patient. Even when we provided a recent review of the OHTS results and written handouts, ophthalmologists had difficulty in accurately predicting the probability of glaucoma in representative patients. This creates a barrier to applying data from large clinical trials, such as the OHTS, to individual patients. The Institute of Medicine recommends that clinicians practice evidence-based medicine by using the results of large randomized clinical trials when treating their patients.[8] Using an available and easily understood risk calculator may decrease the barrier of complexity by simplifying the risk estimate of glaucoma.

Previous Risk Assessment Equations for Glaucoma

Over 20 years ago, Kass et al[11] noted the potential benefits of a risk equation to predict which ocular hypertensive patients are most likely to develop glaucoma. Hart et al[12] found that a logistic regression equation containing vertical C/D, initial IOP, family history of glaucoma, and age was able to classify correctly 97% of ocular hypertensive eyes that developed glaucoma and 80% of eyes that did not. However, this study probably overestimates the predictive ability as it was a retrospective, nonrandomized, observational study in a university setting. The Collaborative Study developed a multiple logistic equation to predict which glaucoma suspects were likely to develop a Goldman visual field abnormality; however, its predictive ability was poor.[13] Nonetheless, these previous attempts show that statistical analysis can be used for risk assessment of the ocular hypertensive patient.

Caveats of Ocular Hypertension Risk Assessment

A recent study suggests that in a critical care setting, clinicians may not change their treatment on the basis of a risk calculator.[14] This randomized, clinical trial showed that even when a risk model predicted an ICU patient would die within a week, doctors rarely used this information to obtain an end of life recommendation from the family.[14] The authors of the study suggested that the doctors were unwilling to apply results from the calculator owing to ''inertia'' and ''lack of incentives'' with the current situation. Presumably, implementation of risk assessment would differ between a critical care setting and an ophthalmologist's office. But the point remains that simply providing a risk assessment tool does not guarantee adoption by clinicians.

Risk assessment and calculation has several other limitations. Risk calculators are based on the best available information, thus their use should be restricted to patients that are similar to the inclusion criteria of the study. For example, with regards to a risk calculator on the basis of OHTS, ophthalmologists should not assume that eyes with secondary causes of ocular hypertension, such as pseudoexfoliation or pigmentary dispersion syndrome, will have similar risk factors to the OHTS study population. Clinicians need to understand that a risk calculator provides a mean risk based on a group of patients with similar characteristics. Rare combinations in OHTS such as a C/D less than 0.2, an IOP above 29 mm Hg, or an age of above 70 years, will result in larger confidence intervals around individual estimates and therefore less precise estimates.[15] At this time, we are unable to provide confidence intervals for the risk calculator estimates because this would require access to the OHTS database to create covariance matrixes and confidence intervals.

Currently available risk calculators[7,16] will likely be refined as more data becomes available from OHTS and other studies such as the European Glaucoma Prevention Study.[17] Although the OHTS equation used in the current study was validated in another patient population,[7] generalizability could be improved by validating the risk estimate in other countries, ethnic groups, and other representative patients. For example, the OHTS patients were recruited from university-based practices and may not represent a typical ocular hypertension patient in an eye care provider office. They may have a lower probability of developing glaucoma because the OHTS patients received free medications and clinical visits, were reliable visual field takers, and were apparently compliant with their medications and follow-up. These characteristics are important to a research study, but uncommon in the clinical realm.

Another manuscript highlights the caveats of risk calculators in general.[18] Two variables of the current risk calculator require further mention. The relevance of diabetes as a protective factor has been questioned because the OHTS entrance criteria created a highly selected population of diabetics, which are unlikely to be representative of most diabetic patients with ocular hypertension.[3] Also, PSD is highly variable and needed to be averaged over multiple baseline visual fields.[3] This variability would create larger confidence intervals for individual estimates. However, using PSD and diabetes in the current study should not affect the variability estimates of the ophthalmologists because all representative patients were not diabetic and had a PSD of 1.9. Future analyses may compare the predictive value of risk calculators with and without including diabetes and PSD.

In addition, the risk calculator demonstrates a difference of 6.8% and 5.2%, respectively in the risk of glaucoma when one changes diabetic status from yes to no, and increases PSD by 2 standard deviations (while keeping the remainder of the characteristics at the OHTS

averages). This suggests that even if diabetes and PSD create variation (or higher confidence intervals) in the risk calculator results, the variation in the risk calculator estimate would be less than the range of the estimates of the surveyed ophthalmologists. Similarly, determination of C/D is variable among ophthalmologists,[19] but this variability would be less than the range of estimates found in the current study.

Overall, the OHTS slide set probability estimates had a lower estimate of risk when compared with the estimate obtained from the risk calculator. These estimates were preliminary, based on a logistic regression model including C/D, age, IOP, and corneal thickness. It did not include PSD or diabetes, and was not based on a Cox proportional hazard model, which explains some of the difference in estimates. The OHTS investigators never published the equation because of the low number of end points and the possibility of unstable estimates (Personal communication, Mae Gordon, May 2006).

Deciding to Treat on the Basis of Risk Estimates

Another important finding of the current study was that even when ophthalmologists had similar estimates of risk, they treated patients differently. This probably reflects the preferences, training, and confidence in the study results of the individual practitioners. As risk assessment is an evolving field and largely new in ophthalmology, eye care providers do not have easily understood guidelines for treating ocular hypertension for various levels of risk. We need expert consensus and cost effectiveness regarding the level of risk appropriate for treating an ocular hypertensive patient.[20,21] Of course, decisions about treatment should not be based solely on the results of a risk calculator or on guidelines for treatment. The risk calculator used in the current study does not include important information guiding treatment such as medical health and life expectancy, patient's willingness to commit to years of eye drops, cost, and the effect of quality of life with treatment. Finally, other randomized controlled trials are needed to confirm the results of OHTS.

Limitations of the Current Study Design

The accuracy of ophthalmologists to predict outcomes in comparison to the true clinical situation may be overestimated by our study design. For example, the ophthalmologists estimated the risk immediately after a recent oral and written review of the results, which decreases the chance that the ophthalmologists would forget the details of the study and their predictive ability may have been higher than ophthalmologists lacking this recent review. Also, the fictitious patients lacked the variety of patient characteristics seen in a clinician's office because they contained differences only in age, IOP, C/D, and corneal thickness, but not in PSD or diabetic status.

We did not randomly select ophthalmologists to participate in the study, but recruited ophthalmologists from continuing medical education programs. The ophthalmologists' characteristics and abilities to predict glaucoma may be different from the general population of clinicians. The current study shows a high range of estimates and while the sample size is only 51 ophthalmologists, a larger sample size or a random sample would be likely to show an even a higher range of estimates. We did not collect any demographic information from the ophthalmologists. Further studies may include differences in predictability on the basis of age, previous knowledge of OHTS results, glaucoma fellowship training, proportion of clinic patients with ocular hypertension, and years since residency.

Summary

The present study examines the ability of ophthalmologists to determine the risk of developing glaucoma from ocular hypertension. Predicting the development of glaucoma from ocular hypertension is a cornerstone to decide on whether or not to treat. Our study showed that ophthalmologists had high variability in the risk estimates, which may result in over and under treatment. Risk calculators may be an innovative approach to simplify the management of ocular hypertension patients and provide evidence-based treatment of ocular hypertension. However, eye care providers should recognize that risk assessment is still evolving and requires refinement. Therefore, eye care providers should consider the result of a risk calculator as supplemental information when deciding whether an ocular hypertension patient needs to be treated.

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