Development of a risk chart to predict who will develop occludable angles in 5 years: the Liwan Eye Study

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Abstract

The presence of an occludable drainage angle in the eye is one of the criteria to diagnosing a patient with primary angle closure glaucoma, a disease that accounts for the blindness of millions of people worldwide. We aimed to generate a risk chart to predict who will develop occludable angle (OA) in 5-years time using age and central anterior chamber depth (ACD) as parameters. Data from adults aged 50 years or older who participated in the baseline and a 5-year follow up visit were analyzed. Logistic regression was used to assess the significance of the age-ACD interaction effect on the risk of OA development. Linear Discriminant Analysis was used as the prediction model for generating the risk chart of OA development and validated by comparing it to the gonioscopic OA diagnosis results from the 5-year follow-up. The risk charts suggested that, for patients with a shallow ACD, risk of OA could increase drastically as patients aged. The risk chart gives reasonable prediction accuracy for dynamically tracking the risk of OA development over the course of 5 years. There is a significant interaction effect between age and anterior chamber depth on the risk of developing OA.

Introduction

It is estimated that 11.1 million people will be bilaterally blind in 2020 due to primary glaucoma, and about 10 million in China alone will have developed primary angle closure glaucoma. Primary angle closure glaucoma accounts for
the vast majority of glaucoma caused blindness in China.\textsuperscript{2} Because the presence of an occludable drainage angle is one of the criteria to diagnosing a patient with primary angle closure glaucoma, it comes as no surprise that risk factors and associated parameters for the development of occludable angle have been researched extensively.

It has been established by prior literature that shallow central anterior chamber depth is associated with increased age and female gender.\textsuperscript{3-5} It has also been shown that increased age and female gender are risk factors for occludable drainage angles.\textsuperscript{6,7} However, most of the evidence is derived from cross-sectional studies and have not proved the value of using these risk factors in the prediction of OA development in the future, not to mention the interaction among these known risk factors.

In clinical practice, gonioscopy is required to detect an occludable angle. Unfortunately, gonioscopy, as an examination, is time consuming and highly dependent on trained glaucoma specialists. Performing gonioscopy for every single patient is not realistic in clinical practice. Therefore, the use of ACD as a first-step non-contact screening tool for identifying OA and angle closure has been proposed.\textsuperscript{8-10} However, the efficacy of using ACD as a risk factor to predict the future development of OA has not yet been attempted. On the other hand, solely considering ACD values is not particularly useful because its distribution is age and gender specific, and ACD is generally shallower in older age and for
females. It would be clinically useful to develop a “risk chart” that encompasses
the use of age, gender, ACD as well as their interactions to predict the presence
of an occludable angle.

We therefore plan to plot risk scores to create a population-based risk chart that
illustrates a patient’s risk of occludable angle development using age and anterior
chamber depth. By separating the risk map into probability zones, a clinician can
quickly and easily visualize not only the patient’s present risk, but also track and
project how that risk will change in future years. A comparable method was used
successfully in the Framingham Heart Disease study, where the risk of
developing coronary heart disease was predicted using algorithms that included
multiple proven associated risk factors such as sex, blood pressure, and
smoking.\textsuperscript{11,12}

In this paper, the ACD data from the Liwan Eye Study data set at baseline was
used to generate a prediction algorithm and to validate its performance on
predicting the development of occludable angle cases at a 5-year follow-up visit.

**Methods**

**Participants**

The Liwan Eye Study was a population-based, cross-sectional study initiated at
baseline, details of which have been reported elsewhere.\textsuperscript{13} In brief, 1405
participants older than 50 years of age were enrolled from the Liwan district of
Guangzhou, China. All participants in the baseline study were invited to take part in the 5-year follow-up examination. The 5-year follow-up examination was conducted November 2009, following the same protocol as the baseline examination.

The baseline data was used for statistical analysis of the interaction effect, and for the prediction model estimation. Of the original 1405 subjects, 67 subjects had undergone cataract surgery and were excluded from the study. 111 subjects with missing OA diagnosis results and/or ACD measurements were also excluded, leaving 1227 subjects for the statistical analysis of the baseline subjects.

Of the 1405 baseline participants, 173 died, 64 moved away, and 112 were unable to be contacted, leaving 1056 eligible follow-up subjects. 924 among the eligible 1056 (87.5%) returned for the follow-up examination at the 5-year mark. Of the 924 returning subjects, those who had already developed OA at baseline (88 subjects) were excluded from the validation analysis. This is because the performance of the prediction model calculating the risk of OA development within a 5-year timespan was validated by using participants who had not developed OA at baseline. Additionally, subjects with inconsistent/missing age or OA diagnosis information at the 5-year follow-up were excluded (220 subjects), leaving 616 subjects for validation analysis at the 5-year follow-up.

The study was conducted in accordance with the tenets of the World Medical
Association’s Declaration of Helsinki. Ethical approval was obtained from the Zhongshan University Ethics Review Board and the Research Governance Committee of Moorfields Eye Hospital in London, England. Written informed consent was obtained from all subjects.

Measures

Central anterior chamber depth and central corneal thickness measurements were taken using an optical pachymetry device (Device I and II, Haag-Streit) that was mounted on a slit lamp (Model 900, Haag-Streit). The “touch method” was used when taking central corneal thickness measurements using Device I at 1.6 objective magnification and the 2.5-diopter eyepiece addition. Readings were taken to the nearest 0.01 mm. The “initial” anterior chamber depth, here defined as the distance between the anterior corneal epithelial surface to the anterior lens capsule, was measured using Device II at 1 objective magnification and the 6-diopter eyepiece addition. The measurement was taken to the nearest 0.05 mm. The measurement was taken three times and the median value was recorded. The corneal thickness measurement was subtracted from the “initial” ACD measurement to calculate the true ACD value. There was no correction made for the corneal curvature.

Gonioscopy was the first biometric measurement taken, using a Goldmann-style one-mirror lens (Model 902; Haag Streit, Bern, Switzerland) set at 25x magnification and low ambient illumination. A 1 mm vertical beam was offset
vertically for nasal and temporal quadrants, and horizontally for superior and inferior quadrants. Extra precaution was taken to avoid light falling on the pupil and the test was performed in a standard dark room with ambient light <5 Lux. Small movements of the lens were deemed acceptable to view the drainage angle, but larger movements was deemed unacceptable and avoided due to the possibility of indentation. The protocol and classification of the geometric angle width estimation has been reported in detail elsewhere.\textsuperscript{14} For our study, an occludable/narrow angle was defined as an eye with an angle where 270 degrees of the pigmented posterior trabecular meshwork was obscured during static gonioscopic examination. The gonioscopy was performed by an experienced fellowship trained specialist (M.H.) throughout.

**Statistical Analysis**

The significance of the Age-ACD interaction effect on the risk of OA can be defined as whether each predictor variable, age and ACD, has an isolated effect on the response variable, OA, or whether the relationship is dependent on values of the other predictor variable. To test which of the two cases was more accurate statistically, logistic regression and the likelihood ratio test were used to assess the significance of the Age-ACD interaction effect on the risk of OA. In logistic regression analysis, age was log-transformed to eliminate skewness. To allow for easier interpretation of the effect size of age and ACD, age and ACD were scaled to have zero mean and standard deviation 1 prior to model fitting. Logistic regression was first performed to evaluate the potential associations between OA
and explanatory variables age, gender, ACD, and age-ACD interaction.

The OA risk chart based on the prediction model was constructed using Linear Discriminant Analysis (LDA). In this analysis the predictor variables Age and ACD were included, with the addition of the Age-ACD interaction variable, as the previously performed logistic regression analysis had proven it to be statistically significant and therefore worthy of inclusion to the LDA model. Briefly, LDA provides a conditional probability model for OA given age, ACD, and age*ACD, i.e. P(OA|age, ACD, age*ACD). The LDA models are constructed using the baseline data. For validation, the OA risks at the 5-year follow-up for subjects without OA at baseline were evaluated using the LDA models. To do this, a subject’s ACD at baseline and age at 5-year follow-up were inputted into the LDA model, and the LDA model would then accordingly output an OA risk score. Males and females were analyzed separately for sex-specific Age-ACD interaction effect, and sex-specific LDA prediction models were also constructed for sex-specific predictions.

A cutoff value between 0 and 1 must be determined for making predictions using the fitted LDA model, such that subjects with risk score larger than the cutoff will be classified as at-risk for OA. For this purpose we employed the Youden Index approach, which chooses the cutoff that maximizes the sum of sensitivity and specificity.15
All statistical analysis was performed using R statistical software version 3.1.2 (Vienna, Austria).

**Results**

The baseline data contains 695 females and 532 males. The mean age among the female subjects was 64.7 yr (standard deviation 9.8 yr). The mean age for the male subjects was 64.8 yr (standard deviation 9.7 yr). No significant age difference was found between the two genders (T-test, p-value=0.95).

The gender variable was considered insignificant (p-value=0.18). Regardless of the insignificance of gender, males and females were still analyzed separately below, along with a combined analysis using subjects with both genders. Table 1 presents the logistic regression analysis of the age-ACD interaction effect. For males, the Age-ACD interaction effect was significant (coefficient=1.416, p-value=0.001). For females, however, this interaction effect does not achieve statistical significance (coefficient=0.473, p-value=0.061). In short, this means that age affects OA development differently at different values of ACD. In the same way, ACD affects OA development differently at different numerical values of age. In this way, it is a statistically complex relationship, but the addition of this interaction term to our model broadens what was already known regarding these variables, and the inclusion of this interaction effect increases the accuracy of the LDA model.
Two candidate classifiers, LDA and logistic regression, were both considered as potential models to create the OA risk status charts of the subjects at the 5-year follow-up based on their ACD at baseline. Table 2 illustrates the breakdown of area under the curve (AUC) comparisons for the LDA classifier versus the logistic regression classifiers. LDA clearly outperforms logistic regression. We therefore chose LDA as our classifier for what follows.

Figure 1 presents the ROC curves for the LDA classifiers for males, females, and both genders combined. These plots also indicate where the cutoff points (determined using the Youden index) are located on the ROC curve. All three classifiers achieve high accuracies (AUC=0.878 for males, 0.839 for females, and 0.858 for both genders) and offer good discrimination. Table 3 presents the predictive performance of LDA for various risk probability cutoffs. Based on the Youden index cutoff, LDA achieved lower sensitivity and higher specificity for males than females. The PPV and NPV were, however, similar for males and females. Classification performance measures for two other cutoffs (0.5 and 0.7) are also presented in Table 3 for reference.

Figure 2 presents the risk charts for OA diagnosis based on the LDA classifier, the plot sectioned into deciles of OA development risk given a patient's present ACD and age. The male risk chart and the female risk chart are similar. To interpret this risk chart, consider a female subject whose ACD is approximately 2.3 mm at age 53 years old (right plot of Figure 2). Her risk of OA is relatively low.
at this age, but as she is located within the risk \(\sim 0.2\) zone, her risk of OA will increase dramatically in 10 years, falling into the risk \(\sim 0.5\) zone. In this way, there is a dynamic functionality of this risk chart.

**Discussion**

An inverse association between ACD, age, and female gender has been reported in a previous study using the baseline Liwan Eye Study data set.\(^{14}\) However, what our research shows, and has not been demonstrated in any prior study, is that a risk chart that integrates the age-ACD interaction is able to achieve reasonably good prediction for OA development in 5-year. This finding is particularly relevant given the established literature that age and ACD are associated.\(^{6-8}\) Additionally, it has been proposed that associations lie between ACD and axial length,\(^{6,7}\) refractive error,\(^{4,14}\) and gonioscopic angle width.\(^{14}\)

However, a clinician, even an ophthalmologist, may find it difficult to incorporate ACD, age and gender to create a risk profile to predict OA development in clinical practice. Our study has isolated two variables that are known to be associated with OA development, and further investigated their statistical relationship and proven that the effect of age on OA development is contingent on ACD. In the same way, the effect of ACD on OA development is contingent on the age of the individual. This can potentially alter how clinicians perceive the relationship between age, ACD, and the risk of OA development, and encourage an evaluation that takes the age-ACD interaction into account.
The second part of this study includes the use of linear discriminant analysis to create the prediction model for the risk of OA and for generating the risk charts. Although this model is certainly population-specific, it is the first to propose a prediction algorithm that can output an OA risk score. This, in a clinical sense, is quite a useful tool. By the ISGEO classification, the presence of an occludable angle is a necessary criterion for the classification of a primary angle closure suspect (PACS). A patient with a raised IOP and/or peripheral anterior synechiae (PAS) in addition to an occludable angle is usually classified as having primary angle closure (PAC). Moreover, other proposed classification systems other than ISGEO also utilize the presence of an occludable angle as criterion for PAC, on which the diagnosis of primary angle closure glaucoma (PACG) is based.

Clearly, the detection of an occludable angle is important for the proper diagnosis of PACS, PAC, and PACG based on the currently accepted classification systems. Gonioscopy is currently the "gold-standard" for identifying an occludable drainage angle and those at risk for PACG, however, there are several drawbacks to this technique. Gonioscopy is a subjective measurement that requires highly trained personnel to operate and so it is of limited use in screening. Therefore alternative methods of screening PACG patients have been proposed, namely, the use of ACD to screen for those at risk of PACG. A visual risk chart of OA development will further improve the performance of the practice of solely using ACD by showing a patients current OA risk, as well as their predicted risk for
future years, all before even undergoing a gonioscopy examination

An extensive amount of research has been done in the Mongolian population regarding the prophylactic treatment of using laser iridotomy (LI) in subjects with occludable angles to reduce the incidence of PACG. Their studies confirmed the traditional belief that in drainage angles less than or equal to Shaffer grade 2, with a 20 degree angle width and only trabecular meshwork is visible, PAC becomes a significant possibility in east Asians. Continuing studies such as the one mentioned above demonstrates the importance of the detection of OA in the prevention of PACG, and our risk chart is a pragmatic method that can supplement current procedures for detecting the risk of developing OA. As more research continues to be done to track the incidence and effectiveness of different treatment options, it becomes increasingly more important to standardize OA classification, and understand the interaction effects that play a role in OA development.

When we compare the diagnostic efficacy derived from the current study with other previous studies that use ACD and peripheral chamber depth as a screening tool for identifying OA in the population, it may be noted that the absolute values of sensitivity and specificity are not as high compared to other studies. However, it is prudent to stress that the diagnostic performance of our current study is for the prediction of future incident OA cases rather than identifying OA cases at the same visit using the current ACD and chamber depth
measurements, which is what has been done in all other studies. Our study suggests that the LDA chart is able to correctly identify at least 69%-79% of the incident OA cases and specify correctly 80%-90% of non-OA cases. Further studies to generate a risk profile chart for predicting who will develop primary angle closure or primary angle closure glaucoma in 5-years could have been more useful but the current dataset does not allow this attempt because the sample size on these diseases are not sufficient.

One limitation of this study is that our results and analysis are population-specific. This sample was taken from the Liwan district of Guangzhou city in urban southern China, and the cohort may not be representative of other ethnic groups and populations. Further studies in other areas or ethnic groups to validate our findings would be valuable in demonstrating how accurate our study results are when compared to those of other geographic areas.

Another limitation of this study is that the central ACD was the only measurement considered in our analysis and the generation of our risk chart. For this cohort a simple assessment of peripheral ACD was carried out based on the percent of corneal thickness (the van Herick technique). Although central ACD is a significant associative factor in OA development and primary angle closure, studies have shown that peripheral and limbal ACD offer a good or even enhanced ability to screen for PACG or detect gonioscopically occludable angles. The incorporation of peripheral or limbal chamber depth to our data
could potentially enhance what we know about the age-ACD interaction effect.

In summary, our study shows that it is possible to generate a risk chart delineating decile risk zones for OA development. Secondly, it offers statistical backing that the effect of age and ACD, variables known to influence OA development, is not an isolated relationship, rather, they are variables dependent on each other that influence of outcome of OA development. The linear discriminant analysis gives reasonable prediction accuracy for OA development given that our model predicts whether OA will develop 5-years into the future from a patient's baseline visit. Because our study is the first to document this, further studies and investigation are necessary in order to validate our findings.

References


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**Author Contribution Statement**

M.G.H. designed the experiments, provided critical reagents and supervised the study. G.F.H. supervised the study and proofread the manuscript. C.A.Y. wrote and proofread the manuscript. B.H.W.C performed the experiments, provided statistical expertise and proofread the manuscript. W.Y.H performed some of the experiments. L.Q.X. performed some of the experiments. X.X.G. proofread the manuscript and performed some of the experiments.

**Competing financial interests:** The authors declare no competing financial
Figure 1. ROC curves and the location of the cutpoints determined by the Youden Index. Brackets above the curves indicate (1-Specificity, Sensitivity) of the cutpoint. The AUC scores and their 95% confidence intervals are presented on the lower-right corners.
Figure 2. The risk charts for male and female based on LDA. The right plot is annotated with an arrow, specifying how the risk of OA for a female subject with ACD ~2.3mm and age 63yr may drastically increase in 10 years.

Table 1. Summary of Logistic Regression Analysis

<table>
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<th></th>
<th>Male</th>
<th>Female</th>
<th>Both Genders</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Regression Coefficient</td>
<td>$P$</td>
<td>Regression Coefficient</td>
</tr>
<tr>
<td>Intercept</td>
<td>-5.892</td>
<td>0.003</td>
<td>-3.203</td>
</tr>
<tr>
<td>Age</td>
<td>1.711</td>
<td>0.003</td>
<td>0.808</td>
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<tr>
<td>ACD</td>
<td>-3.723</td>
<td>&lt;0.001</td>
<td>-2.413</td>
</tr>
<tr>
<td>Age x ACD</td>
<td>1.416</td>
<td>0.001</td>
<td>0.473</td>
</tr>
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</table>

P-values computed using Likelihood Ratio Test.

Table 2. AUC Analysis

<table>
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<th>Female</th>
<th>Both Genders</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>AUC</td>
<td>95% CI</td>
<td>AUC</td>
</tr>
<tr>
<td>LR</td>
<td>0.133</td>
<td>(0.07, 0.20)</td>
<td>0.83</td>
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<tr>
<td>LDA</td>
<td>0.878</td>
<td>(0.82, 0.94)</td>
<td>0.84</td>
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</table>

Abbreviation: AUC = area under curve, CI = confidence interval, LDA = linear discriminant analysis, LR = logistic regression.
Table 3. Predictive Performance for OA at 2009 based on the Linear Discriminant Analysis.

<table>
<thead>
<tr>
<th>Cutoff</th>
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<th>Female</th>
<th>Both Genders</th>
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<tbody>
<tr>
<td></td>
<td>0.26*</td>
<td>0.5</td>
<td>0.7</td>
</tr>
<tr>
<td>Acc</td>
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<td>0.87</td>
<td>0.89</td>
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<tr>
<td>Sens</td>
<td>0.69</td>
<td>0.50</td>
<td>0.47</td>
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<tr>
<td>Spec</td>
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<td>0.92</td>
<td>0.95</td>
</tr>
<tr>
<td>PPV</td>
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<td>0.47</td>
<td>0.54</td>
</tr>
<tr>
<td>NPV</td>
<td>0.96</td>
<td>0.93</td>
<td>0.93</td>
</tr>
</tbody>
</table>


* Cutoff determined by the Youden Index.