Biometric Risk Factors for Angle Closure Progression after Laser Peripheral Iridotomy: The Zhongshan Angle Closure Prevention Trial

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Short Title: Post-laser Biometry Predicts Angle Closure Progression

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Key Points

Question: What biometric factors predict development of severe angle closure disease in primary angle closure suspect (PACS) eyes after treatment with laser peripheral iridotomy (LPI)?

Findings: In this retrospective analysis of data from the Zhongshan Angle Prevention Trial (ZAP) Trial, PACS eyes with persistent angle narrowing by anterior segment OCT (AS-OCT) or cumulative gonioscopy score two weeks after LPI were at significantly higher risk of primary angle closure (PAC) and acute angle closure.

Meaning: AS-OCT or gonioscopy can be performed after LPI to identify patients at higher risk for severe angle closure disease who may benefit from closer monitoring.

ABSTRACT

Importance: Laser peripheral iridotomy (LPI) is the most common primary treatment for primary angle closure disease (PACD). However, there is sparse data guiding the longitudinal care of primary angle closure suspect (PACS) eyes after LPI.

Objective: To elucidate the anatomical effects of laser peripheral iridotomy (LPI) that protect against progression from PACS to primary angle closure (PAC) and acute angle closure (AAC), and to identify biometric factors that predict progression of PACS eyes treated with LPI.

Design, Setting, Participants: This is a retrospective analysis of data from the Zhongshan Angle Prevention (ZAP) Trial, a study of mainland Chinese aged 50 to 70 years with bilateral PACS who received LPI in one randomly selected eye. Gonioscopy and AS-OCT imaging of both eyes were performed 2 weeks after LPI. Progression was defined as development of primary angle closure (PAC) or an acute angle closure (AAC) attack. Cohort A included a random mix of treated and untreated eyes, and Cohort B included only eyes treated with LPI. Univariable and multivariable Cox regression models were developed to assess biometric risk factors for progression in Cohorts A and B.

Main Outcome and Measure: Six-year progression to PAC or AAC.

Results: Mixed Cohort A included 878 eyes (44 progressors) of 878 participants. In univariable analysis, treatment with LPI was protective against progression (HR=0.40, p=0.006). In multivariable analysis, treatment (p=0.25) was no longer associated with progression after adjusting for age (HR=1.08 per 1 year older, p=0.03) and $TISA_{500}$ (HR=1.33 per 0.01 mm^2 smaller, p<0.0001) at the 2-week visit. Cohort B included 869 treated eyes (19 progressors). In multivariable analysis, $TISA_{500}$ (HR=1.33 per 0.01 mm^2 smaller, p=0.001) and cumulative gonioscopy score (HR=1.25 per grade smaller, p=0.02) at the 2-week visit were associated with progression. Persistent angle narrowing on AS-OCT ($TISA_{500}$≤0.05 mm^2; HR=9.41) or gonioscopy (cumulative score≤6; HR=2.80)) conferred higher risk of progression (p≤0.02).

Conclusions and Relevance: Persistent angle narrowing by AS-OCT or cumulative gonioscopy score are predictive of disease progression in PACS eyes after LPI. AS-OCT and gonioscopy can be performed to identify high-risk angle closure patients who may benefit from closer monitoring despite patent LPI.

Introduction

Primary angle closure glaucoma (PACG) is a significant cause of permanent vision loss, currently affecting around 20 million people worldwide.[1] Although primary open angle glaucoma (POAG) is more common than PACG, PACG is around 2.5 times more likely to cause blindness than POAG.[2] Angle closure occurs when there is obstruction of the trabecular meshwork by the peripheral iris, which impedes outflow of aqueous humor through the anterior chamber angle.[3] This process can lead to elevated intraocular pressure (IOP) and glaucomatous optic neuropathy. Primary angle closure disease (PACD) occurs on a spectrum, progressing from primary angle closure suspect (PACS) to primary angle closure (PAC) to primary angle closure glaucoma (PACG).[4] Treatment with laser and lens extraction surgery can alleviate angle closure, lower intraocular pressure (IOP), and reduce risk of developing PACG.[5–7] While there is consensus on the treatment of eyes with PAC and PACG, the benefit of treating PACS eyes is less clear.[8,9] Therefore, ongoing research in the field of angle closure is focused on identifying predictive factors to guide care of PACS eyes.[10]

The most common primary treatment for angle closure is laser peripheral iridotomy (LPI), a procedure that creates an alternative pathway for aqueous flow between the anterior and posterior chambers. LPI widens the angle by relieving pupillary block, a key anatomical mechanism underlying angle closure.[11,12] The Zhongshan Angle-Closure Prevention (ZAP) Trial, a landmark study on angle closure, found that LPI effectively halves the risk of progression from PACS to PAC or acute angle closure (AAC) over a 6-year period.[7] While it is intuitive that this lowered progression risk is related to the angle widening effects of LPI, this has not been demonstrated experimentally. The ZAP Trial also found that progression still occurred in LPI-treated eyes at a rate of 0.4% per eye year.[7] While narrower angle width and flatter iris curvature predict angle closure progression in untreated PACS eyes, it is unclear if these risk factors extend to PACS eyes after LPI treatment.[10]

In this study, we use data from the ZAP Trial to assess the role of anterior segment OCT (AS-OCT) and gonioscopy in evaluating PACS eyes after treatment with LPI. First, we assess biometric factors that are associated with angle closure progression in treated versus untreated eyes, which could help elucidate

the protective mechanism/s of LPI. We also assess which biometric factors predict progression of PACS eyes after LPI. While biometric predictors of anatomical changes after LPI are well-studied, biometric predictors of longitudinal clinical outcomes (e.g. more severe PACD) after LPI remain unclear.[13]

Methods

The ZAP Trial was approved by the Ethical Review Board of Sun Yat Sen University, the Ethical Committee of Zhongshan Ophthalmic Center, and the Institutional Review Boards of Moorfields Eye Hospital and Johns Hopkins University. The University of Southern California Institutional Review Board approved the present study. All study procedures adhered to the Declaration of Helsinki, and all study participants provided written informed consent.

Data for the current study were derived from the ZAP Trial, a single center randomized controlled trial conducted in Guangzhou, China. In brief, the ZAP Trial recruited participants aged 50 to 70 years with bilateral PACS, defined as eyes with 2 or more quadrants of non-visibility of pigmented TM on manual gonioscopy, in the absence of PAS, IOP more than 21 mmHg, and glaucomatous optic neuropathy. One eye per participant was randomized to treatment with LPI. The other eye was monitored without treatment and served as the control eye. Participants underwent complete baseline examinations prior to LPI treatment, including AS-OCT imaging, gonioscopy, and ultrasound A-scan biometry. Participants were re-examined 2 weeks after the baseline visit. Gonioscopy and AS-OCT data used in this study was derived from the 2-week visit to capture the effects of LPI. Study endpoints included the development of PAC, which was defined as IOP >24 mmHg on 2 separate occasions, development of 1 or more clock hours of PAS, or an AAC attack.

Static gonioscopy was performed under dark ambient lighting standardized at less than 1 lux illumination (EA30 EasyView Light Meter; Extech Instruments; Waltham, MA, USA) with a 1-mm light beam and a Goldmann-type 1-mirror goniolens (Haag-Streit AG; Köniz, Switzerland) before pupillary dilation. Gonioscopy was performed by one of two fellowship-trained glaucoma specialists with high intergrader agreement (weighted $k > 0.80$).[14] Care was taken to avoid light falling on the pupil, inadvertent

114 indentation of the globe, and tilting of the lens of more than 10º. The angle was graded in each quadrant
115 accordingly: grade 0, no structures visible; grade 1, nonpigmented TM visible; grade 2, pigmented TM
116 visible; grade 3, scleral spur visible; and grade 4, ciliary body visible. Cumulative gonioscopy score was
117 calculated as the sum of gonioscopy grades from all 4 quadrants.

118 AS-OCT imaging was performed along the horizontal (temporal-nasal) and vertical (superior-
119 inferior) meridians with the Visante AS-OCT system (Carl Zeiss Meditec, Inc; Dublin, CA, USA) under
120 dark ambient lighting standardized at less than 1 lux illumination before pupillary dilation. During imaging,
121 eyelids were retracted gently, taking care to avoid inadvertent pressure on the globe. Ultrasound A-scan
122 biometry (CineScan A/B, Quantel Medical, Bozeman, MT, USA) was performed to measure axial length
123 (AXL) and lens thickness (LT).

124

125 ***AS-OCT Image Analysis***

126 AS-OCT images were analyzed using the custom Zhongshan Angle Assessment Program, which
127 automatically segmented anterior segment structures and produced biometric measurements after the scleral
128 spurs were marked.[15] Image analysis was performed by 5 certified graders who were masked to examination
129 results and intervention assignments. Graders confirmed the segmentation and marked the scleral spurs in
130 each image.

131 In total, 13 biometric parameters describing the anterior segment were measured in each AS-OCT
132 image obtained at the 2-week visit. These included angle opening distance 500 and 750 um anterior to the
133 scleral spur (AOD_{500} and AOD_{750}, respectively) trabecular iris space area bounded by AOD_{500} or AOD_{750}
134 ($TISA_{500}$ and $TISA_{750}$, respectively), posteriorly by a line drawn from the scleral spur perpendicular to the
135 plane of the inner scleral wall to the opposing iris, superiorly by the inner corneoscleral wall, and inferiorly
136 by the iris surface; iris thickness at 750 and 2000 um from the scleral spur (IT_{750} and IT_{2000}, respectively);
137 iris area (IA); iris curvature (IC); lens vault; anterior chamber depth; anterior chamber width (ACW);
138 anterior chamber area (ACA); and pupillary diameter (PD). A set of 20 images from 20 eyes was selected

randomly and graded independently by all 5 graders. Intergrader agreement in the form of intraclass correlation coefficients were excellent for all AS-OCT parameters (ICC > 0.83).

Cohort Selection

Cohort A included one eye chosen at random from each ZAP Trial participant who had bilateral progression or non-progression. Among participants with unilateral progression, the eye that progressed to PAC or AAC was selectively chosen for analysis. Cohort A was created using a mix of treated and untreated eyes to elucidate the protective mechanism/s that reduce risk of progression in treated eyes. Cohort B included only treated eyes of ZAP Trial participants. Cohort B was created to assess the clinical and ocular biometric predictors of angle closure progression in post-LPI eyes.

Statistical Analysis

For parameters with two measurements per image (e.g. AOD750), horizontal and vertical measurements of biometric parameters were averaged. Differences between means of continuous variables were compared between progressors and non-progressors using the unpaired t-test, while categorical variables were compared using the chi-squared test. Only horizonal AS-OCT measurements were included in the analyses as vertical measurements of AS-OCT measurements did not significantly differ between progressors and non-progressors with the outcome variable.

Univariable and multivariable Cox regression models were developed to assess the relationships between clinical and biometric parameters assessed 2 weeks after randomization and angle closure progression in a time dependent manner for both Cohorts A and B. Only one AS-OCT measure of angle width was included in multivariable analysis due to multi-collinearity. Although horizontal AOD_{500} and $TISA_{500}$ both demonstrated significant association with progression, $TISA_{500}$ was ultimately included in multivariable analysis due to its smaller p-value in multivariable analysis. Multivariable Models A, B, and C were limited to four variables and Models D, E, and F were limited to two variables due to the number of progressors in Cohorts A (N=44) and B (N=19). Multivariable Models A, B, and C were developed to

elucidate the anatomical effects of LPI that protect against PACS progression. Multivariable Models D, E, and F were developed to identify biometric risk factors for progression. Multivariable Models G, H, and J were developed to assess the association between progression and persistent narrowing after LPI, defined as angle width based on the lowest quartile of angle width based on horizontal $TISA_{500}$ measurements ($\leq$ 0.05 mm^2), gonioscopic angle status (closed = gonioscopy grade 0 or 1 in $\geq$2 quadrants), or cumulative gonioscopy scores ($\leq$ 6). SAS version 9.4 (2020; SAS Institute Inc., Cary, NC). Statistical analyses were conducted using a significance level of 0.05.

Results

Among the 889 ZAP trial participants, 11 participants were excluded due to missing 2-week AS-OCT data. Cohort A included 878 eyes of 878 ZAP Trial participants, of whom 726 were female (82.7%) and 152 (17.3%) were male, with a mean age of 58.9 ± 5.0 years. There were 433 untreated eyes and 445 treated eyes in Cohort A with 44 progressors (13 treated with LPI (29.6%), 31 of whom were untreated (70.4%)). In mixed Cohort A, progressors had significantly ($p \leq 0.03$) older age, smaller cumulative gonioscopy score, and smaller measurements of horizontal AOD_{500}, horizontal AOD_{750}, and horizontal $TISA_{500}$ at the 2-week visit (Table 1). A smaller proportion of PACS eyes that progressed were treated with an LPI compared to PACS eyes that did not progress (29.6% vs 51.8%, p = 0.004).

In mixed Cohort A, univariable Cox regression models showed that older age was associated with progression (HR = 1.07 per year older, p = 0.04), whereas treatment with LPI was protective (HR = 0.40, p = 0.006). Greater horizontal AOD_{500} (HR = 0.86 per 0.01 mm), horizontal AOD_{750} (HR = 0.91 per 0.01 mm), horizontal $TISA_{500}$ (HR = 0.71 per 0.01 mm^2), and cumulative gonioscopy score (HR = 0.74 per 1 grade) at the 2-week visit were also protective ($p < 0.04$) against progression (Table 2).

In multivariable Model A (Time-Dependent Area Under the Receiver Operating Characteristic Curve (tdAUC = 0.75 at 72 months)), older age (HR = 1.08 per 1 year, p = 0.03) and smaller horizontal $TISA_{500}$ (HR = 1.33 per 0.01 mm^2, $p < 0.0001$) at the 2-week visit were associated with progression, whereas treatment with LPI (p = 0.25) was no longer protective (Table 2). In multivariable Model B (tdAUC= 0.74

191 at 72 months), older age (HR = 1.08 per 1 year, p = 0.02) and smaller cumulative gonioscopy score (HR =
192 1.43 per 1 grade, p < 0.0001) at the 2-week visit were associated with progression, whereas treatment with
193 LPI (p = 0.34) was no longer protective (Table 2). In multivariable Model C (tdAUC= 0.79 at 72 months),
194 older age (HR = 1.08 per 1 year, p = 0.01), smaller cumulative gonioscopy score (HR = 1.32 per 1 grade, p
195 = 0.004), and smaller horizontal $TISA_{500}$ (HR = 1.33 per 0.01 mm^2, p < 0.0001) measured at the 2-week
196 visit were associated with progression, whereas treatment with LPI (p = 0.29) was no longer associated
197 (Table 2).

198 Cohort B included 869 treated eyes of 869 ZAP Trial participants, of whom 717 (82.5%) were
199 female and 152 (17.5%) were male, with a mean age of 58.9 ± 5.0 years. Twenty participants from the
200 original 889 were excluded due to missing AS-OCT data. Among this cohort of 869 eyes treated with LPI,
201 there were 19 progressors.

202 In treated Cohort B, progressors had significantly smaller horizontal AOD_{500}, horizontal AOD_{750},
203 horizontal $TISA_{500}$, horizonal $TISA_{750}$, and cumulative gonioscopy scores and larger lens vault two weeks
204 after LPI than non-progressors (p < 0.05 for all, Table 3).

205 In multivariable Model D (tdAUC= 0.76 at 72 months), among eyes treated with LPI, smaller
206 horizontal $TISA_{500}$ (HR = 1.39 per 0.01 mm^2, p < 0.0001) was associated with progression, whereas age
207 was not associated (p = 0.06; Table 4). In multivariable Model E (tdAUC = 0.69 at 72 months), smaller
208 cumulative gonioscopy score (HR = 1.39 per 1 grade, p < 0.0001) was associated with progression, and age
209 was not associated (P = 0.08; Table 4). In multivariable Model F (tdAUC = 0.78 at 72 months), smaller
210 cumulative gonioscopy score (HR = 1.25 per 1 grade, p = 0.02) and horizontal $TISA_{500}$ (HR = 1.33 per 0.01
211 mm^2, p = 0.001) were associated with progression (Table 4).

212 In multivariable Models G, H, and J, the effects of persistent angle narrowing were assessed (Table
213 5). In multivariable Model G (tdAUC = 0.79 at 72 months), horizontal $TISA_{500}$ ($\leq$ 0.05 mm^2) in the lowest
214 quartile (25.0%) after LPI was predictive of progression (HR = 9.41, p < 0.0001). The progression rate of
215 eyes with TISA $\leq$ 0.05 mm^2 was 1.15% per eye year compared to 0.15% per eye year in eyes with TISA >
216 0.05 mm^2. In multivariable Model H (tdAUC = 0.62 at 72 months), the lowest quartile of gonioscopic angle

status (closed) approached but did not reach significance (p = 0.08). In multivariable Model J (tdAUC= 0.68 at 72 months), cumulative gonioscopy score (≤ 6) in the lowest quartile (25.2%) was predictive of progression (HR = 2.80, p = 0.04). The progression rate of eyes with cumulative gonioscopy score ≤ 6 was 4.1% per eye year compared to 1.5% per eye year in eyes with cumulative gonioscopy score > 6.

Discussion

In this study, we used data from the ZAP Trial to demonstrate that LPI protects against progression from PACS to PAC or AAC primarily through its angle widening effect, and that among LPI-treated eyes, smaller angle width and cumulative gonioscopy score 2 weeks after LPI are independent predictors of progression. Our findings provide insight into the protective mechanism of LPI and establishes the utility of AS-OCT and gonioscopic assessments of angle width for identifying eyes at higher risk of angle closure progression after LPI.

The presumed anatomical benefit of LPI is relief of pupillary block, which leads to angle widening, reduction of IOP, and decreased risk of angle closure progression.[7,12,13,16,17] However, the protective mechanism of LPI for reducing progression risk had not been demonstrated experimentally prior to this study. In the univariable analysis of treated and untreated eyes, treatment with LPI was strongly and significantly protective against progression. However, in the multivariable analysis, when LPI treatment status was adjusted for post-LPI horizontal $TISA_{500}$ or cumulative gonioscopy score, treatment was no longer associated with progression. This suggests that it is primarily the angle widening effect of LPI that protects PACS eyes from progression. Interestingly, when all three of these factors were included in a single model, both horizontal $TISA_{500}$ and cumulative gonioscopy score remained significant predictors of progression, while suggests that AS-OCT and gonioscopy provide independent information that may be useful for predicting progression when performed after LPI.

Although LPI reduced the risk of progression by 47% in the ZAP Trial, treated eyes still progressed to a study endpoint at a rate of 0.4% per eye year, highlighting the need to identify factors associated with progression in these eyes.[7] While smaller angle width and flatter iris curvature were predictive of

progression in untreated PACS eyes, it was unclear if these anatomic risk factors were conserved after LPI.[10] In the univariable analysis of LPI-treated eyes, AS-OCT measurements of angle width and cumulative gonioscopy score after LPI were predictive of progression; however, iris curvature was not. The significant risk conferred by narrower angle width regardless of treatment status is intuitive; narrower angles increase the risk of iridotrabecular contact and obstruction of aqueous outflow. The lack of association between iris curvature and progression risk after LPI could be explained by the iris-flattening effect of LPI and a convergence of iris profiles overall.[18] In addition, other anatomical mechanisms of angle closure, including plateau iris configuration and anteriorized lens likely predominate in determining progression risk after pupillary block is relieved.[19,20]

There is sparse evidence to guide longitudinal care of PACS eyes after treatment with LPI. Guidelines published by the American Academy of Ophthalmology recommend repeat gonioscopy after LPI, although the precise rationale behind this recommendation is unclear.[8] There is no recommendation to perform AS-OCT imaging before or after LPI. Previous studies identified biometric factors that predicted longitudinal anatomical changes; however, it is difficult to base practice patterns on anatomic outcomes measures alone.[21,22] Our study provides the first evidence that progression of disease from PACS to PAC or AAC can be predicted by persistent angle narrowing on AS-OCT and gonioscopy 2 weeks after LPI: a horizontal $TISA_{500} \leq 0.05$ mm^2 or a cumulative gonioscopy score ≤ 6 after LPI conferred 9.41 and 2.80 times higher risk of progression, respectively, whereas persistent gonioscopic angle closure alone did not predict progression. The progression rate among eyes with persistent angle narrowing on AS-OCT was 1.15% per eye year, which exceeds the rate observed even among untreated eyes (0.8% per eye year). In contrast, progression was exceedingly rare among treated eyes without persistent angle narrowing on AS-OCT (0.15% per eye year). These findings support the clinical utility of measuring angle width with AS-OCT or at least assessing cumulative gonioscopy score after LPI; however, the same may not hold true for simply identifying the angle as open or closed. By extension, eyes with persistent angle narrowing by AS-OCT measurements or cumulative gonioscopy score after LPI may benefit from long-term monitoring, whereas eyes without persistent angle narrowing may not.

While AS-OCT measurements of angle width at the 2-week visit were predictive of progression in both LPI-treated and untreated eyes, cumulative gonioscopy score was only predictive in LPI-treated eyes.[10] This finding highlights differences between AS-OCT and gonioscopic angle assessments and provides insight into when each method provides clinically useful information. While AS-OCT measurements of angle width and cumulative gonioscopy score are well correlated overall, they are poorly correlated among angle closure eyes.[23,24] In addition, IOP appears to be better correlated with AS-OCT measurements of angle width than gonioscopy grades.[25,26] The disagreement between AS-OCT and gonioscopy in eyes with narrow angles is likely related to factors independent of angle width that make visualization of the trabecular meshwork on gonioscopy more difficult, such as high iris curvature or shallow anterior chamber depth.[27,28] In the case of progression among PACS eyes, gonioscopic assessments of angle width appear to be more useful for risk-stratification when there is a wider range of angle widths (e.g. post-LPI eyes) than a narrower range (e.g. untreated eyes).

Older age is a well-established risk factor for more severe PACD and PACS progression in untreated eyes.[29] The effect of older age was not statistically significant in univariable or multivariable analyses of post-LPI eyes. The lack of significance could be related to our relatively small number of treated progressors (N=19), causing our analysis to have insufficient power to capture the effect of age. Nevertheless, age-related changes in ocular biometrics, such as increased lens thickness and lens vault and decreased anterior chamber depth, contribute to progression of angle closure and remain an important factor in the management of post-LPI eyes. [17–19]

Our study has several limitations. First, there were a relatively low number of progressors in our analysis of LPI-treated eyes (N = 19). This limited our multivariable analysis to two variables and may have prevented us from identifying other significant but weakly predictive factors. However, this is an inherent limitation of longitudinal studies on progression from PACS to PAC or AAC, which remains a rare event, especially after LPI treatment. Second, our relatively simple multivariable models predicting progression produced only moderate predictive performance. The development of more robust models, perhaps using machine learning methods, may help with more precise detection of high-risk eyes. Finally, our study

population is comprised of only Chinese between age 50 to 70 years with bilateral PACS and clear lenses or non-visually cataracts. Our findings may not be generalizable to other demographic groups or patients with more severe angle closure and/or cataracts.

In conclusion, this study highlights the importance of post-LPI angle assessments and provides initial evidence toward establishing clearer guidelines about long-term monitoring of PACS eyes after primary treatment with LPI. These topics merit further investigation as LPI remains the first-line treatment for many patients with PACD without visually significant cataracts, despite recent trends moving away from LPI and toward earlier lens extraction.[5–7] Further research directed toward optimizing anatomical outcomes after LPI may also be beneficial for delivering precision care to patients with PACS patients and mitigating the risk of PACG-related blindness.

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Table and Figure Captions

Table 1: Differences in clinical and biometric measures between progressors and non-progressors among a mixed sample of treated and untreated eyes at 2 weeks after LPI (Cohort A).

Table 2: Univariable and multivariable Cox regression models of clinical and biometric predictors of progression among a mixed sample of treated and untreated eyes at 2 weeks after LPI (Cohort A).

Table 3: Differences in clinical and biometric measures between progressors and non-progressors among treated eyes at 2 weeks after LPI (Cohort B).

Table 4: Univariable and multivariable Cox regression models of clinical and biometric predictors of progression among treated eyes at 2 weeks after LPI (Cohort B).

Table 5: Age-adjusted Cox regression models of the association between angle closure progression and categorical measures (lowest quartile) of horizontal $TISA_{500}$, gonioscopic angle status, and cumulative gonioscopy score among treated eyes at 2 weeks after LPI (Cohort B).