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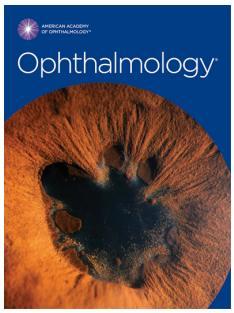

14-Year Outcome of Angle-Closure Prevention with Laser Iridotomy in the Zhongshan Angle Closure Prevention Study: Extended Follow-Up of a Randomized Controlled Trial

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14-Year Outcome of Angle-Closure Prevention with Laser Iridotomy in the Zhongshan Angle Closure Prevention Study: Extended Follow-Up of a Randomized Controlled Trial

Running Title: The Zhongshan Angle Closure Prevention Trial

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Abbreviations and Acronyms:

ZAP = Zhongshan Angle Closure Prevention; RCT = randomized controlled trial; LPI = laser peripheral iridotomy; PACS = primary angle-closure suspect; PAC = primary angle closure; PACG = primary angle-closure glaucoma; AAC = acute angle closure; PAS = peripheral anterior synechiae; DRPPT = dark-room prone provocative test; LACD = limbal anterior chamber depth; CACD = central anterior chamber depth; HR = hazard ratio; 95%CI = 95% confidence interval; IOP = intraocular pressure; ACD=anterior chamber depth; UBM = ultrasound biomicroscopy; AUC=area under the receiver operating characteristic curve.

Key Words: primary angle closure; laser peripheral iridotomy; extended follow-up

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Abstract

Purpose: This study aimed to evaluate the efficacy of laser peripheral iridotomy (LPI) prophylaxis for primary angle closure suspects (PACS) after 14 years and to identify risk factors for the conversion from PACS to primary angle closure (PAC).

Design: An extended follow-up of Zhongshan Angle Closure Prevention (ZAP) study.

Participants: A total of 889 Chinese patients aged 50 to 70 years with bilateral PACS.

Methods: Each patient received LPI in one randomly selected eye, with the fellow untreated eye serving as a control. Since the risk of glaucoma was low and acute angle closure (AAC) only occurred in rare cases, the follow-up was extended to 14 years despite substantial benefits of LPI reported after the 6-year visit.

Main Outcome Measures: The primary outcome was incidence of PAC, a composite endpoint including peripheral anterior synechiae (PAS), intraocular pressure (IOP) > 24 mmHg, or AAC.

Results: During the 14 years, 390 LPI-treated eyes and 388 control eyes were lost to the follow-up. A total of 33 LPI-treated eyes and 105 control eyes reached primary endpoints (P <0.01). Within them, twelve eyes developed AAC or primary angle closure glaucoma (AAC: five control eyes and one LPI-treated eye; PACG: four control eyes and two LPI-treated eyes). The hazard ratio for progression to PAC was 0.31 (95% confidence interval, 0.21–0.46) in LPI-treated eyes compared with control eyes. At the 14-year visit, LPI-treated eyes had severer nuclear cataract, higher IOP, larger angle width and limbal anterior chamber depth (LACD) than control eyes. Higher IOP, shallower LACD, and central anterior chamber depth (CACD) were associated with an increased risk of developing endpoints in control eyes. In the treated group, eyes with higher IOP, shallower LACD, or less IOP elevation after dark room–prone provocative tests (DRPPT) were more likely to develop PAC after LPI.

Conclusions: Despite a two-third decrease in PAC incidence after LPI, the cumulative risk of PAC was relatively low in the community-based PACS population over 14 years. Apart from IOP, IOP elevation after DRPPT, CACD, and LACD, more risk factors are needed to achieve precise prediction of PAC occurrence and guide clinical practice.

Introduction

Primary angle closure glaucoma (PACG) is one of the most significant irreversible blinding eye diseases worldwide.[1] It is estimated that more than 32 million patients would suffer from PACG until 2040, of which about three-quarters are Asians. In China, approximately 28.2 million patients with suspicion of primary angle closure and 9.1 million patients with primary angle closure (PAC) may develop PACG.[2] Prophylactic laser peripheral iridotomy (LPI) has traditionally been recommended for primary angle closure suspects (PACS) to prevent angle closure. However, considering the large-scale population at risk for PACG, mass laser intervention is an expensive proposition that requires strong evidence to endorse this as a massive prophylactic strategy.[3, 4]

The Zhongshan Angle Closure Prevention (ZAP) Study is a randomized clinical trial (RCT) that enrolled 899 bilateral PACS participants from Guangzhou, China. With one eye treated by LPI and the other remaining untreated as a control, the ZAP Study showed that LPI achieved a 50% reduction in the 6-year risk of PAC progression in PACS.[5] More recently, the Singapore Asymptomatic Narrow Angles Laser Iridotomy Study (ANA-LIS) further confirmed the aforementioned findings in the context of Singaporean hospitals.[6]

Although identifying risk factors associated with the increased risk of developing PAC is an objective of both of these two studies, [7-9] it is under power to explore prophylactic effects within different groups and develop prediction models due to the low event rates observed in the 6-year study. Therefore, we extended the study and completed a 14-year follow-up period for the ZAP Study to report (1) the level of LPI that reduces the risk of endpoint events among PACS in the long term, and (2) the natural course of PACS over time, as well as risk factors related to PAC progression.

Methods

Design, Participants, and Procedures of the ZAP Study

The ZAP Study was a single-center randomized controlled trial, and its protocol has been published previously.[5, 9] Briefly, 11,991 community residents aged 50–70 years were screened for biliteral PACS (invisible pigmented trabecular meshwork with ≥ 6 clock hours under static gonioscopy) in Guangzhou, China. Exclusion criteria included peripheral angle synechiae (PAS), intraocular pressure (IOP) >21mmHg, corneal opacity, visual impairment (<20/40), history of intraocular surgeries, penetrating ocular trauma, or acute angle closure (AAC) characterized by anterior segment abnormalities including iris whirling, glaucomfleken, or excessive trabecular pigment deposition. In addition, patients with IOP elevation over 15 mmHg after the dark-room prone provocative test (DRPPT) were deemed as at risk of AAC and also excluded. For each eligible participant, one eye was randomly selected to be treated with LPI, and the other eye was kept untreated as a control. The LPI was conducted by a trained ophthalmologist using the Abraham lens (Ocular Instruments, Bellevue, WA, USA). Yd:YAG laser (Visulas YAG III, Carl Zeiss Meditec, Dublin, CA, USA) with a starting energy setting of 1.5 mJ and a minimum diameter of 200 μm spot was used, targeting the crypt or the thinnest of iris, which could be obscured by the upper lid during eye opening. Except for baseline examinations, treated and untreated eyes were examined at 2 weeks and then at 0.5, 1.5, 3, 4.5 and 6 years after the LPI intervention in the 6-year ZAP trial.

Examinations and Outcomes in a 14-Year Extended Study

After the 6-year visit, all participants were informed that the risk of vision impairment due to AAC or PACG was extremely low and it was not necessary to receive prophylactic LPI in the control eye based on existing evidence. Until the 14-year visit, all living participants of the ZAP study were invited to this extended follow-up with the same examination protocols. The extended study was approved by the Zhongshan Ophthalmic Center Ethical Review Committee and performed in accordance with the Declaration of Helsinki. All participants signed informed consent forms before enrollment and each follow-up.

Using a Goldmann-type single-mirror gonioscope (Ocular Instruments, Bellevue, WA, USA), static gonioscopy was performed in a standard dark environment (< 1 lux)

with a narrow 1-mm beam. The angle widths between the surface tangent of the trabecular meshwork and the peripheral third volume of the iris were assessed using the Shaffer grading system in each quadrant. The angle widths were recorded for five classification points (Shaffer grading 0–4 representing 0°, 10°, 20°, 30°, and 40° angle widths). If the forward bulging of the iris made observation of the angle difficult, it was allowed to tilt the gonioscope slightly (<10°) to determine whether it was open or not. If trabecular meshwork was not visible, the presence of PAS was determined by dynamic examination with a four-mirror gonioscope (Ocular Instruments, Bellevue, WA, USA). If iridotrabecular contact could be restored by compression, then the patient was considered to have PACS and was eligible for enrollment. Gonioscopy was performed by glaucoma specialists with standardized training and > 10 years of experience (weighting κ values > 0.80).

Presenting visual acuity was measured using the Early Treatment Diabetic Retinopathy Study logarithm of the minimum angle of resolution E-chart (Precision Vision, Villa Park, IL, USA). The IOP was first assessed using Goldmann applanation tonometry by a trained nurse who was unaware of the LPI treatment. Three IOP measurements were recorded at each visit, and the average value was calculated. In the DRPPT, a Tono-Pen applanation tonometer (Tono-Pen XL, Medtronic, FL, USA) was used to measure IOP before and after a 15-minute lying in the dark room (< 1 lux) with foreface down. Ocular biometric parameters, including central anterior chamber depth (CACD) and lens thickness, were measured by ultrasound A-scan biometry (CineScan A/B; Quantel Medical, France) after topical anesthesia. 24-2 Fast visual field tests were carried out in both eyes using Humphrey Field Analyzer HFA-II, (Carl Zeiss Meditec, Dublin, CA, USA). Repeated tests were required if false positive or negative error was larger than 33%. The limbal anterior chamber depth (LACD) was assessed using a modified van Herick grading method with a slit lamp (BQ-900, Haag-Streit, Switzerland). The depth of the temporal anterior chamber at the corneoscleral junction was expressed as a percentage of the adjacent corneal thickness. For examination of the lens, optic disk, macula, and peripheral retina, 0.5% tropicamide and 5% phenylephrine eye drops were used to dilate the pupil. The Lens

Opacity Classification System III was used to grade cataracts with reference to standard photographs. Lens color and opalescence, cortical cataracts, and posterior subcapsular cataracts were assessed using six, five, and five retro- illumination images, respectively.

The primary outcome was the risk of developing PAC, consisting of the following three study endpoints: (1) IOP > 24 mmHg confirmed by a re-check on another day within one week, (2) PAS ≥ 1 clock hour in either quadrant, or (3) AAC. The secondary outcomes were presenting visual acuity, IOP, total angle width on gonioscopy, LACD, central anterior chamber depth (CACD), lens thickness, and cataract grading scores. The development of PACG was further diagnosed based on glaucomatous optic neuropathy together with visual field defects.

Statistical Analyses

The analyses of primary outcomes were based on the intention-to-treat (ITT) principle, which included randomly assigned patients, and the per-protocol (PP) principle was adopted for the sensitivity analysis. Baseline characteristics were compared between different groups using within-subject analyses of variance and chi-square tests. The efficacy of LPI to prevent PAC progression was assessed using the McNemar test, which is based on fractional intervals and continuity corrections. Kaplan–Meier survival curves were used to show event rates, and log-rank tests were used to test the equilibrium of the survival curves. To account for both time and events between LPI-treated eyes and control eyes, univariable and multivariable Cox proportional hazards regression models were built to evaluate the association of LPI intervention and PAC occurrence, which reported hazard ratios (HRs) and 95% confidence intervals (CIs) after adjusting for baseline covariates. Data for eyes that underwent cataract surgeries were removed at the last follow-up visit before cataract surgeries. In sensitivity analyses, competing-risk Cox regression was performed with cataract surgeries treated as a competing risk. Logistic regression models were also built, which only included eyes that reached the primary endpoints or were censored at the 14-year visit. Based on significant risk factors, univariable and multivariable

Logistic models were built to predict the 14-year occurrence of PAC in control eyes and LPI-treated eyes, respectively. Predictive efficacy was assessed using the area under receiver operating characteristic curve (AUC). For each risk factor, the optimal cutoff value was determined by Youden index. Sensitivity, specificity and categorical odds ratios (ORs) beyond the cut-off value were reported. Secondary outcomes were compared between LPI-treated eyes and control eyes using paired *t*-tests. All statistical analyses were performed using Stata version 15.1. The significance level of the two-sided test was set at 0.05. The trial was registered on the ISRCTN registration platform (ISRCTN45213099).

Results

From 2008 to 2022, a total of 899 eligible participants received LPI intervention in a randomly selected eye and participated in the follow-up. **Figure 1** illustrates the flow process of the study. The mean age of the enrolled patients was 59.3 ± 5.0 years, and 737 (83%) of the participants were women. The comparison of baseline characteristics had been reported in previous studies, which were balanced between LPI-treated eyes and control eyes. [5, 9] This was the 14-year extended follow-up of ZAP study, which was completed in 499 (56.13%) and 501 (56.36%) of the 889 eyes in the treatment and control groups, respectively. The mean duration of follow-up was 8.70 (SD 4.91) years in the LPI-treated eyes and 8.69 (SD 4.92) years in the control eyes. Patients that refused or were lost to follow-up were significantly older and had higher IOP at baseline. A total of 70 LPI-treated eyes and 54 control eyes received cataract surgeries before the 14-year visit or endpoints. Except for being older, eyes receiving cataract surgeries also had lower IOP, severer nuclear, cortical and posterior subcapsular cataract than the remaining eyes at baseline (**Table S1**).

Until the 14-year visit, 33 LPI-treated eyes (4.27 eyes per 1000 eye-years) and 105 control eyes (13.59 eyes per 1000 eye-years) reached the primary endpoint (**Table 1 and 2**). After adjusting for the inter-eye correlations, the primary outcome between the treated and untreated eyes remained significant using McNemar's

pairwise tests in the ITT analysis ($P < 0.01$). The PP analysis was performed by excluding participants who lost to the follow-up, who had cataract surgeries, and who had LPI in the control eyes, of which the results were consistent (**Table 1**). We also analyzed the primary outcome using a Cox model, and the risk of reaching the endpoint was reduced by 69.9% in the LPI-treated eyes (HR: 0.31; 95% CI: 0.21–0.46; **Figure 2**). Accordingly, the number needed to treat (NNT) was 12.35 (95%CI: 9.42-17.67) to prevent one PAC occurrence over 14 years.

The benefit of treatment was mainly achieved by reducing the development of PAS (LPI, 3.62 per 1000 eye-years vs. control, 12.68 per 1000 eye-years; NNT:12.70, 95%CI: 9.71-18.05; $P < 0.01$; **Table 2**). In LPI-treated eyes, the proportion of PAS ≥2 clock hour was slightly lower than that in control eyes (4/28, 14.3%; 28/98, 28.6%; $P = 0.33$). Compared to baseline measurements, PVA, total angle width score, and LACD were slightly decreased in PAS eyes ($P <0.01$). By contrast, IOP was moderately increased after PAS formation (15.75 ± 2.88 vs. 16.42 ± 3.20 mmHg; P = 0.02), with IOP ≥21 mmHg only found in 11 (8.73%) PAS eyes (**Table S2**). IOP elevation ≥24 mmHg was uncommon in both groups (LPI, 0.52 per 1000 eye-years vs. control, 0.78 per 1000 eye-years; NNT=444.50; $P = 0.53$). Within the 10 eyes reaching the IOP endpoint, PAS ≥1 clock hour was found in three control eyes, and one eye had PAS ≥2 clock hour. Only one LPI-treated eye and five control eyes had AAC (LPI, 0.13 per 1000 eye-years vs. control, 0.65 per 1000 eye-years; NNT: 222.25; $P = 0.10$), with PAS ≥2 clock hours found in one control eye. PACG was diagnosed in two LPI-treated eyes and four control eyes, with biliteral PACG found in one patient (**Table S3**). At the 14-year visit, LPI-treated eyes had larger angle width (7.63 ± 3.02 vs. 2.04 ± 2.60; $P < 0.01$) and LACD (29.97 ± 11.06 vs. 14.91 ± 7.63; $P < 0.01$) compared with the control eyes. There were also statistical differences found in IOP and nucleus cataract degrees, which were both slightly higher in LPI-treated eyes ($P < 0.01$). No statistical difference was found in other secondary outcomes at the 14-year visit (**Table S4**).

In univariable models, the increased risks of PAC occurrence were found in eyes with higher IOP, narrower angle width, shallower LACD and CACD at baseline. In multivariable models adjusting for all covariates (the mean variance inflation factor =

1.12), IOP (per 1 mmHg higher HR: 1.12, 95% CI: 1.05–1.18), LACD (per 10% higher HR: 0.64, 95% CI: 0.49-0.82) and CACD (per 1 mm higher HR: 0.89, 95% CI: 0.82-0.98) were significantly associated with the increased risk of PAC occurrence over 14 years (**Table 3**). In subgroup analyses, associations between IOP and LACD with PAC occurrence remained statistically significant in both control eyes and LPI-treated eyes, respectively (**Table 4**). On the contrary, CACD was only significantly associated with PAC occurrence in control eyes. In treated eyes, less IOP elevation after DRPPT was significantly associated with the increased risk of PAC (per 1 mmHg higher HR: 0.87, 95% CI: 0.77-0.97), which was different from its counterpart in control eyes (P for interaction with LPI <0.05). These findings were also supported by competing-risk models (**Table S5**) and Logistic regression models (**Table S6 and S7**). Determined by Youden index, cut-off values of IOP, LACD, CACD and IOP changes after DRPPT allowed preliminary stratification for eyes with 2-3 times higher PAC risks (**Table 5**). To predict PAC occurrence over the 14 years in control eyes, multivariable Logistic models consisting of IOP, LACD, CACD provided better performance than univariable models (AUC: 0.70, 95%CI: 0.64-0.76). IOP, LACD, IOP elevation after DRPPT, and their combination had similar performance in LPI-treated eyes (AUC: 0.62-0.71).

Discussion

Principal Findings

To the best of our knowledge, the ZAP study remains the largest single-center clinical trial to provide evidence for better preventive treatment decisions in patients at risk of developing primary angle closure. Eyes treated with LPI had a 69% reduced risk of developing PAC, with much of this difference owing to a nearly threefold higher incidence of PAS in the control eyes. Even after up to 14 years of extended follow-up, the rate of events that reached the endpoint remained quite low. In the untreated eyes, increased IOP, decreased LACD, and CACD at baseline were significantly associated with the risk of reaching the endpoint. In the treated eyes, lower level of IOP elevation after DRPPT at baseline was identified as an additional risk factor for primary endpoints.

Natural History of PACS

Few longitudinal studies have described the natural history of PACS eyes. In the Indian population, Thomas et al. reported a 5-year conversion rate from PACS to PAC of 22%;[10] however, the credibility of the data has been questioned, as this incidence was derived from only 82 PACS patients. Ye et al. followed 485 patients with PACS for 6 years and found that 20 (4.1%) cases progressed to PACG. [11] In the Inuit population, Wilensky et al. followed 129 cases of PACS, and found that 25 (19.4%) cases developed PAC during a mean of 2.7 years of follow-up.[12] In the recent Singapore Epidemiology of Eye Diseases Study, which included 222 patients with PACS over 6 years of follow-up, 9.38% progressed to PAC or PACG.[13] In the population-based Handan Eye Study, which included 526 patients with PACS over 5 years of follow-up, 32 cases progressed (31 PAC and 1 PACG) at a rate of 6.08%.[14] The only study conducted for >10 years reported a 35% progression rate of PACS in Inuits.[15] It is worth noting that the previously mentioned studies used a wide variety of definitions of angle closure. In the ANA-LIS study, 9.4% (21.84 per 1000 eye-years) of PACS had progressed over 5 years of follow-up, compared to the 14-year cumulative risk of in this study (11.81%), which may be related to the hospital-based population and more lenient definitions of endpoints.[6] Notably, the vast majority (98/105) of the eyes that converted to PAC showed evidence of mild PAS, a benign disorder, with about 2%–6% of PAS eyes progressing to PACG annually.[16, 17] In this study, IOP increases >21 mmHg were found in only 7 control eyes (7.14%) at PAS diagnoses. After laser or cataract surgeries, most PAS eyes diagnosed within the first 6 years could remain stable over the long term. Until the 14-year visit, only four control eyes developed to PACG and needed further anti-glaucoma treatments.

Efficacy of Prophylactic LPI

Both paired tests and Cox models demonstrated that LPI reduced the incidence of PAC by approximately two-thirds. The only direct comparable data were the ANA-LIS study, which also focused on patients of Chinese ethnicity.[6] Within the 5-year follow-up for the ANA-LIS, LPI was significantly associated with a 45% reduced risk of

PAC progression in PACS patients. The event rates for IOP elevation and AAC were extremely low and not significantly different between LPI-treated eyes and control eyes in both studies, which suggests that the risk of acute episodes in patients with PACS was substantially lower than initially expected before the LPI intervention. Despite NNT dropped to 12.35 after the extended 14-year follow-up, prophylactic LPI should be preferentially recommended to those at the highest risk of angle closure because the annual incidence of PAC was low and AAC/PACG were relatively rare in the community-based PACS population over the long-term. This study also proved the long-term safety of LPI intervention, with similar visual acuity found between LPI-treated eyes and control eyes. Despite higher degrees of nuclear cataract found in treated eyes, prophylactic LPI led to only 16 additional cataract surgeries in 889 PACS patients (17.12 ‰) during the 14 years. Considering that more than two thirds of cataract surgeries occurred six years after the LPI, its effect on long-term cataract progression and relevant clinical significance should be ascertained in further studies. Similar with 6-year findings, a slightly higher IOP was found in treated eyes at the 14-year, which might be attributed post-LPI inflammation responses and dynamic changes of aqueous humor outflow. Nevertheless, the mere 0.34 mmHg elevation of IOP found in LPI-treated eyes was unlikely to affect established protective effects of LPI, as a secondary finding in those without PAC occurrence.

Risk factors for the Natural Progression of PACS

The higher number of events that occurred over a long follow-up period potentially allowed us to identify those at high risks of progression to PAC. We found that both LACD and CACD were potential risk factors for naturally rapid PACS progression, which is consistent with the results of previous studies. In the Handan Eye Study, logistic regression analysis found that baseline angle width was associated with progression.[14] Another study in a Mongolian population indicated that narrow angles diagnosed by grading LACD and gonioscopy were strongly associated with the occurrence of an occludable angle.[18] Another study including 75 patients with PACS in the Greenland subgroup found that LACD (25%) and CACD (2.7 mm) could

effectively discriminate a subgroup that is at risk of developing PACG over 10 years.[19] Previous studies have demonstrated that van Herick examination is highly reproducible between observers, and our prior analysis showed a sensitivity of 98.2% for the diagnosis of PACS with LACD grading at a 25% cutoff.[20] Another important risk factor was baseline IOP, which was consistent with the ANA-LIS results that eyes with higher IOP were likelier to arrive at the endpoints.[6]

Risk factors for PAC occurrence after LPI

It was reported that 11–25% of eyes with PACS remained persistently closed after LPI.[21] In the Liwan Eye Study, 19.4% of PACS eyes remained closed on gonioscopy after LPI treatment, and ultrasound biomicroscopy (UBM) revealed that 59% of eyes had ≥ 1 quadrant of iridotrabecular contact.[22, 23] In a hospital-based study, about 22% of Vietnamese patients progressed to PAC within 11-year follow-up after LPI.[24] Another hospital-based study found that approximately 28% of PACS progressed to PAC within two years of undergoing LPI.[25] In the ANA-LIS study, 81.8% of participants had residual angle closure of ≥ 2 quadrants under gonioscopy at one year after LPI, which was related to greater iris volume and higher IOP. Our study further confirmed that patients with lower LCAD and higher IOP at baseline were more likely to develop PAC even after LPI, which represented occludable angles and compromised aqueous humor outflow.[6] Notably, we found that less IOP elevation after DRPPT was an independent risk factor for PAC progression after LPI. Given the fact that DRPPT was generally used to stimulate pupil block mechanism [26] and LPI removed the pupil block mechanism, the observed marginal statistically significant association between DRPPT and primary endpoints among LPI eyes was likely spurious. This is consistent with the findings that DRPPT is unable to discriminate PACS patients from those at risk of PAC progression in the previous studies.[12, 27]

Strengths and Limitations

This study has several advantages. First, the "split-body design," in which one eye is randomized to treatment and the other eye serves as a control, reduces

individual-level confounding factors. Second, there was a sufficiently long follow-up period to observe the outcomes of the events or events of interest. Third, the sample size of the study was large, and the level of effort required to run such a long-term follow-up trial with high retention rates was substantial. Modeling PACS- and LPI-treated eyes separately, we also explored potential risk factors for PAC occurrence.

This study has some limitations. First, patients at high risk for PACS were excluded, such as those with previous episodes of acute attack in either eye or those with a DRPPT > 15 mmHg. Therefore, the endpoint rate derived from the trial might underestimate the actual morbidity rate. Second, about 45% participants dropped out the 14-year follow-up and quite a few patients underwent cataract surgery. The role of cataract surgery in the management of patients with PACS should be investigated in future RCTs. Third, the effects of corneal thickness, daytime IOP fluctuations, and family history of PAC on the outcomes were not assessed.[3] Fourth, only the Chinese population was included, and the results cannot be directly generalized to patients of other ethnic groups. Last but not least, efficacy of IOP, CACD, LACD and DRPPT in the prediction of PAC occurrence was not satisfactory. To further improve the predictive performance, detailed quantification of anterior chamber structures based on anterior segment optical coherence tomography and UBM are warranted in the future.

Conclusion

In summary, the 14-year ZAP study demonstrated that LPI significantly reduced the risk of PAC occurrence in PACS eyes by two-thirds over the long-term, which further confirmed previous six-year results and supported the suggestion that LPI-free observation is an alternative to PACS. Considering that the occurrence rate was relatively low and asymptomatic PAS consisted of the majority of PAC cases, prophylactic LPI should be primarily prescribed for the high-risk population. Although baseline IOP, IOP change after DRPPT, LACD, and CACD were significantly associated with PAC occurrence in LPI-treated or control eyes, more potent predictors are still

needed to realize precise prediction and guide targeted intervention in the future.

Authorship Contribution:

Research design: Wei Wang, David S. Friedman, Paul J. Foster, Mingguang He;

Research execution: Yixiong Yuan, Wei Wang, Ruilin Xiong, Cong Li, Shaopeng Yang;

Data analysis: Yixiong Yuan, Wei Wang, Zhang Jian, Mingguang He; Manuscript preparation: Yixiong Yuan, Wei Wang, Ruilin Xiong, Zhang Jian, Mingguang He.

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498 **Figure legends**

499 **Figure 1.** Study profile.

500

501 **Figure 2.** Kaplan-Meier failure estimation plot of the study endpoint. Hazard ratio

502 (HR) and 95%CI for laser peripheral iridotomy was 0.31 (0.21, 0.46).

503

Table 1. Pair-wise analysis of the study endpoint at the 14-year visit.

Intention-to-treat analysis		Laser peripheral iridotomy		
		No endpoint	**Endpoint**	**Total**
Control	**No endpoint**	771 (86.73%)	13 (1.46%)	784 (88.19%)
	Endpoint	85 (9.56%)	20 (2.25%)	105 (11.81%)
	Total	856 (96.29%)	33 (3.71%)	889 (100.00%)

Per-protocol analysis		Laser peripheral iridotomy		
		No endpoint	**Endpoint**	**Total**
Control	**No endpoint**	289 (74.87%)	5 (1.30%)	294 (76.17%)
	Endpoint	72 (18.65%)	20 (5.18%)	92 (23.83%)
	Total	361 (93.52%)	25 (6.48%)	386 (100.00%)

Both $P<0.01$ with McNemar's test.

Table 2. Primary endpoints at the 14-year visit by intention-to-treat analysis.

	Laser peripheral iridotomy (n=889)	Control (n=889)	p value
Reach primary endpoint	33 (4.27 per 1000 eye-years)	105 (13.59 per 1000 eye-years)	<0.01
Before 6 years	19	36	
7-14 years	14	69	
Intraocular pressure measures >24mmHg	4 (0.52 per 1000 eye-years)	6 (0.78 per 1000 eye-years)	0.53
Before 6 years	3	5 *	
7-14 years	1	1	
Peripheral anterior synechiae ≥1 clock	28 (3.62 per 1000 eye-years)	98 (12.68 per 1000 eye-years)	<0.01
Before 6 years	15	30	
7-14 years	13	68	
Acute attack	1 (0.13 per 1000 eye-years)	5 (0.65 per 1000 eye-years)	0.10
Before 6 years	1	5 *	
7-14 years	0	0	

All values are number of events unless stated otherwise.
P values were estimated by long-rank tests for equality of survival function.
* Four control eyes reached both peripheral anterior synechiae endpoint and intraocular pressure or acute attack endpoint at the same visit.

Table 3. Cox regression models of the association between baseline factors and primary endpoints at the 14-year visit.

	Eyes that did reach endpoints, n=138, 8%	Eyes that did not reach endpoints, n=1634, 92%	Univariable model		Multivariable model	
			Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
Laser peripheral iridotomy (vs control)	23.91%	52.33%	0.31 (0.21-0.46)	<0.01	0.31 (0.21-0.45)	<0.01
Age, years (per 1 year old)	59.02 (5.07)	59.35 (5.02)	1.02 (0.99-1.06)	0.24	1.02 (0.98-1.06)	0.31
Female (vs Male)	85.51%	82.74%	1.17 (0.73-1.87)	0.52	0.92 (0.56-1.50)	0.73
Baseline intraocular pressure, mmHg (per 1mmHg higher)	15.86 (2.87)	15.03 (2.82)	1.12 (1.06-1.19)	<0.01	1.12 (1.05-1.18)	<0.01
Total angle width, score (per 1 score higher) *	4.75 (2.61)	5.39 (2.36)	0.90 (0.84-0.97)	<0.01	0.96 (0.89-1.03)	0.29
Limbal anterior chamber depth, % (per 10% higher) †	19.60 (8.71)	22.37 (7.49)	0.57 (0.45-0.72)	<0.01	0.64 (0.49-0.82)	<0.01
Central anterior chamber depth, mm (per 0.1 mm higher) ‡	2.50 (0.23)	2.55 (0.22)	0.87 (0.80-0.94)	<0.01	0.89 (0.82-0.98)	0.02
Lens thickness, mm (per 1 mm higher) ‡	4.91 (0.31)	4.87 (0.32)	1.78 (1.00-3.16)	0.05	1.03 (0.54-1.96)	0.94
Dark room prone provocative test, mmHg (per 1mmHg higher)	4.29 (2.97)	4.25 (2.99)	0.99 (0.93-1.04)	0.61	0.97 (0.92-1.03)	0.39

All values are mean (SD) unless proportions of laser peripheral iridotomy treatments and females.

Multivariable Cox regression models include laser peripheral iridotomy, age, gender, baseline intraocular pressure, and variables of interest.

Six eyes with unavailable A-scan results were excluded.

* Total angle width was calculated by the sum of Shafer grading of all four quadrants (range from 0 to 16, larger number indicates wider angle).

† Limbal anterior chamber depth was evaluated by modified van Herick grading.

‡ Central anterior chamber depth and lens thickness were measured by A-scan.

Table 4. Multivariable-adjusted Cox models for the association between baseline factors and primary endpoints at the 14-year visit in control eyes and treated eyes.

	Control (n=884)		Laser peripheral iridotomy (n=888)	
	Hazard ratio (95% CI)	**p value**	**Hazard ratio (95% CI)**	**p value**
Age, years (per 1 year old)	1.01 (0.97-1.06)	0.57	1.03 (0.96-1.11)	0.36
Female (vs Male)	0.95 (0.53-1.68)	0.85	0.86 (0.32-2.29)	0.76
Baseline IOP, mmHg (per 1mmHg higher)	1.11 (1.04-1.19)	<0.01	1.14 (1.02-1.28)	0.03
Total angle width, score (per 1 score higher) *	0.98 (0.90-1.06)	0.60	0.92 (0.79-1.06)	0.24
Limbal anterior chamber depth, % (per 10% higher) †	0.70 (0.52-0.93)	0.02	0.45 (0.27-0.76)	<0.01
Central anterior chamber depth, mm (per 0.1mm higher) ‡	0.88 (0.79-0.98)	0.02	0.94 (0.78-1.13)	0.50
Lens thickness, mm (per 1mm higher) ‡	1.19 (0.56-2.54)	0.65	0.69 (0.21-2.29)	0.54
Dark room prone provocative test, mm Hg (per 1mmHg higher) §	1.01 (0.95-1.08)	0.69	0.87 (0.77-0.97)	0.02

Multivariable Cox regression models include age, gender, intraocular pressure (IOP), and variables of interest.

Six eyes with unavailable A-scan results were excluded.

* Total angle width was calculated by the sum of Shafer grading of all four quadrants (range from 0 to 16, larger number indicates wider angle).

† Limbal anterior chamber depth was evaluated by modified van Herick grading.

‡ Central anterior chamber depth and lens thickness were measured by A-scan.

§ P for interaction<0.05 with laser peripheral iridotomy treatment.

Table 5. Univariable and multivariable Logistic models to predict primary endpoints in control eyes and treated eyes that reached the primary endpoints or were censored at the 14-year visit.

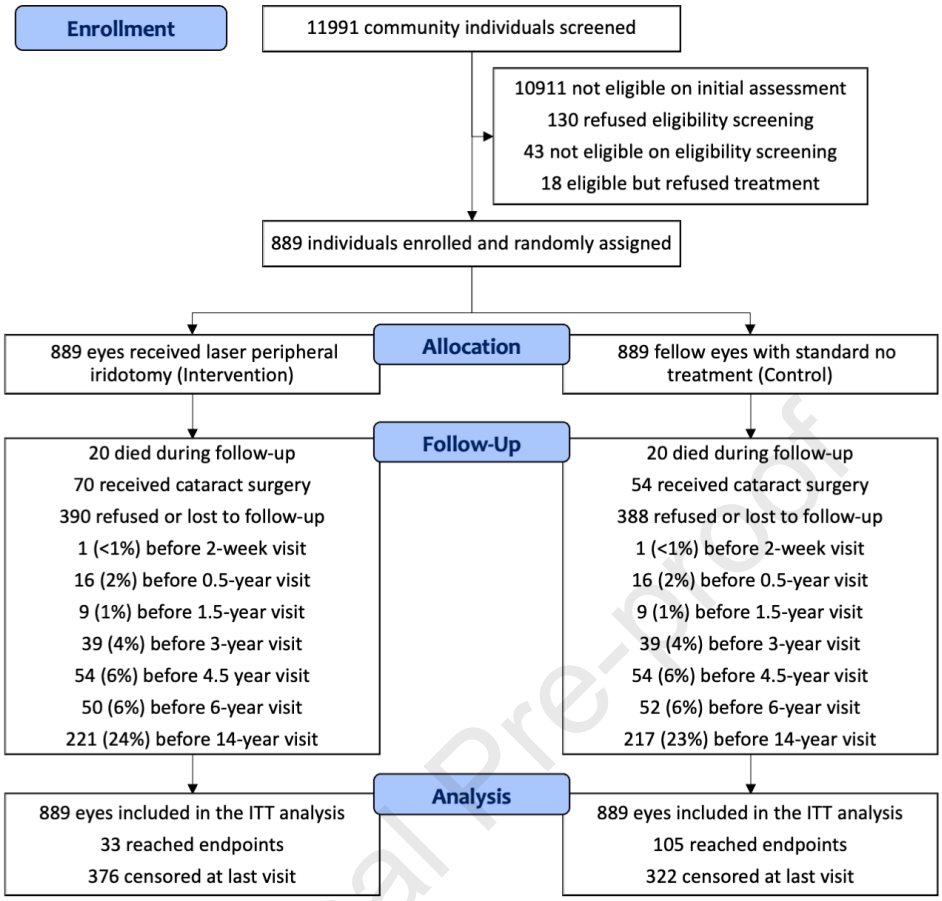
Subgroup	Area under the curves (95% CI)	Optimal cutoff value for variable	Odds values (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Control eyes (N=411)					
Intraocular pressure at baseline	0.60 (0.54-0.66)	>13 mmHg	2.70 (1.48-4.90)	0.85 (0.77-0.92)	0.31 (0.26-0.37)
Limbal anterior chamber depth *	0.61 (0.55-0.67)	≤15%	2.44 (1.54-3.86)	0.49 (0.39-0.59)	0.72 (0.67-0.77)
Central anterior chamber depth †	0.63 (0.56-0.69)	≤2.44 mm	2.41 (1.51-3.85)	0.44 (0.34-0.54)	0.76 (0.70-0.80)
Combined the above 3 parameters	0.70 (0.64-0.76) #	–	–	–	–
Laser peripheral iridotomy treated eyes (N=409)					
Intraocular pressure at baseline	0.62 (0.51-0.72)	>15 mmHg	2.01 (0.97-4.16)	0.61 (0.42-0.77)	0.57 (0.51-0.62)
Limbal anterior chamber depth *	0.65 (0.55-0.75)	≤15%	3.00 (1.46-6.20)	0.58 (0.39-0.75)	0.69 (0.64-0.74)
Intraocular pressure changes after dark room prone provocative test	0.62 (0.52-0.72)	≤4 mm Hg	2.45 (1.14-5.29)	0.70 (0.51-0.84)	0.52 (0.46-0.57)
Combined the above 3 parameters	0.71 (0.61-0.81) #	–	–	–	–

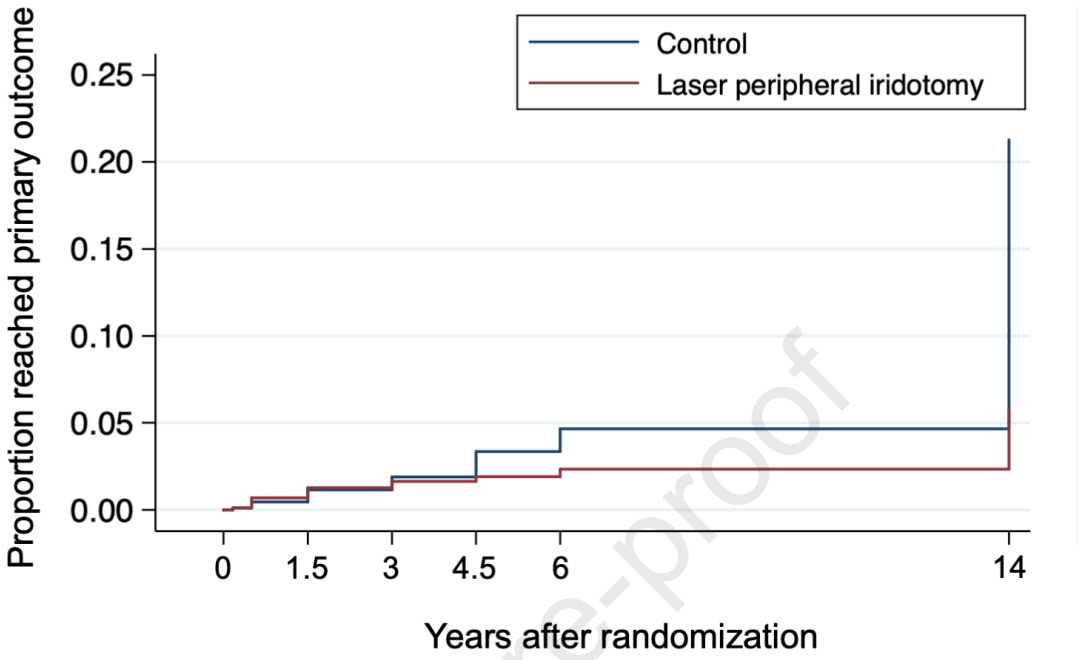
* Limbal anterior chamber depth was evaluated by modified van Herick grading.

† Central anterior chamber depth was evaluated by A-scan.

‡ Bonferroni-corrected P values for the comparison of AUCs between the multivariable model and single risk factors.

The area under curve of multivariable models was significantly higher than those of univariable models in control eyes (all P values <0.05). No significant difference was found between the area under curve of multivariable models and those of univariable models in treated eyes.





Number at risk

Control	857	806	737	662	391
Laser peripheral iridotomy	852	804	741	671	390

Précis

This study found that laser peripheral iridotomy reduced long-term risks of primary angle closure by two-thirds, although its incidence was uncommon over 14 years. Prediction models were warranted to guide prophylactic intervention in high-risk suspects.