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Ocular Biometric Risk Factors for Progression of Primary Angle Closure Disease: The Zhongshan Angle Closure Prevention Trial

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1 **Ocular Biometric Risk Factors for Progression of Primary Angle Closure Disease: The Zhongshan**
2 **Angle Closure Prevention Trial**

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18

19 **Short Title:** Biometric Risk Factors for Angle Closure Progression

20

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27 **ABSTRACT**

28 **Purpose:** To assess baseline ocular biometric risk factors for progression from primary angle closure
29 suspect (PACS) to primary angle closure (PAC) or acute angle closure (AAC).

30 **Design:** Prospective observational study.

31 **Participants:** 643 mainland Chinese aged 50 to 70 years with untreated PACS.

32 **Methods:** Participants received baseline clinical examinations including gonioscopy, anterior segment
33 OCT (AS-OCT) imaging (Visante OCT, Carl Zeiss Meditec, Dublin, CA), and A-scan ultrasound biometry
34 as part of the Zhongshan Angle Closure Prevention (ZAP) Trial. PACS was defined as inability to visualize
35 pigmented trabecular meshwork in two or more quadrants based on static gonioscopy. PAC was defined as
36 development of elevated intraocular pressure (IOP) > 24 mmHg or peripheral anterior synechiae (PAS).
37 Progression was defined as development of PAC or an acute angle closure (AAC) attack. Multivariable
38 logistic regression models were developed to assess biometric risk factors for progression.

39 **Main Outcome Measures:** Progression from PACS to PAC or AAC over 6 years.

40 **Results:** 643 untreated eyes (609 non-progressors, 34 progressors) of 643 ZAP participants were included
41 in the primary analysis. In a multivariable model with continuous parameters, narrower horizontal angle
42 opening distance 500 μm from the scleral spur (AOD500; OR=1.10 per 0.01 mm decrease, $p=0.03$), flatter
43 horizontal iris curvature (IC; OR=1.96 per 0.1 mm decrease, $p=0.01$), and older age (OR=1.11 per year
44 increase, $p=0.01$) at baseline were significantly associated with progression (AUC=0.73). Smaller
45 cumulative gonioscopy score was not associated with progression (OR=1.03 per 1 modified Shaffer grade
46 decrease; $p=0.85$) when replacing horizontal AOD500 in the multivariable model. In a separate
47 multivariable model with categorical parameters, participants in the lowest quartile of horizontal AOD500
48 (OR=3.10, $p=0.002$) and IC (OR=2.48, $p=0.014$) measurements and aged 59 years and older (OR=2.68,
49 $p=0.01$) at baseline had higher odds of progression (AUC=0.72).

50 **Conclusions:** Ocular biometric measurements can help risk stratify patients with early angle closure for
51 more severe disease. AS-OCT measurements of biometric parameters describing the angle and iris are
52 predictive of progression from PACS to PAC or AAC, whereas gonioscopy grades are not.

53 **Introduction**

54 Primary angle closure glaucoma (PACG) is a leading cause of permanent vision loss worldwide, affecting
55 around 20 million people.^{1,2} Angle closure, characterized by apposition between the trabecular meshwork
56 and peripheral iris, is the primary anatomical risk factor for PACG. Primary angle closure suspect (PACS),
57 the earliest stage of angle closure, is diagnosed when multiple quadrants of angle closure are present on
58 gonioscopy.³ PACS progresses to primary angle closure (PAC), which confers a higher risk of PACG, when
59 eyes develop peripheral anterior synechiae (PAS) or elevated intraocular pressure (IOP).⁴⁻⁶ Laser and
60 surgical treatments help alleviate angle closure, which could delay or prevent the progression of PACS and
61 PAC to PACG.^{6,7} Therefore, identifying high-risk angle closure eyes for early intervention is essential to
62 reducing the prevalence of PACG. While the general consensus is that PAC should be treated with laser
63 peripheral iridotomy (LPI) or lens extraction surgery, it is unclear which cases of PACS stand to benefit
64 from treatment.^{8,9}

65 The recent landmark Zhongshan Angle Closure Prevention (ZAP) Trial demonstrated that risk of
66 progression from PACS to PAC or acute angle closure (AAC) is low in mainland Chinese aged 50 to 70
67 years, even in the absence of treatment with LPI.⁶ Based on this finding, we recommended against
68 widespread LPI treatment of PACS eyes. However, without any treatment, more cases of PACS will likely
69 progress to PAC and PACG. This is problematic given that the prevalence of PACG is already expected to
70 rise over the next two decades.² In addition, PACG is associated with high rates of unilateral blindness on
71 initial diagnosis and a three-fold greater risk for severe bilateral visual impairment compared to primary
72 open angle glaucoma (POAG).¹⁰⁻¹³ Therefore, there is an urgent need for clinical tools to identify high-risk
73 cases of PACS that could benefit from early intervention.

74 Ocular biometric parameters measured by anterior segment OCT (AS-OCT) and ultrasound A-scan
75 are established risk factors for angle closure and differ between eyes with open angles, PACS, PAC, and
76 PACG.¹⁴⁻²⁰ A subset of these biometric parameters are also predictive of incident gonioscopic angle closure
77 and anatomical angle narrowing over a 5-year period.²¹⁻²³ While it is reasonable to speculate based on these
78 findings that biometric measurements also predict progression from early angle closure (PACS) to more

79 severe disease (PAC and AAC), this has never been demonstrated experimentally. In fact, there is sparse
80 data to guide clinical management of PACS and no quantitative method to identify patients with high-risk
81 PACS. In this study, we use data from the ZAP Trial to assess biometric risk factors for progression from
82 PACS to PAC or AAC and develop statistical models that could help risk stratify patients with early angle
83 closure for more severe disease.

84

85 **Methods**

86 The ZAP Trial was approved by the Ethical Review Board of Sun Yat Sen University, the Ethical
87 Committee of Zhongshan Ophthalmic Center, and the Institutional Review Boards of Moorfields Eye
88 Hospital and Johns Hopkins University. Ethics committee approval for the current study was also obtained
89 from the University of Southern California Medical Center Institutional Review Board. All study
90 procedures adhered to the recommendations of the Declaration of Helsinki. All study participants provided
91 informed consent at the time of enrollment.

92

93 *Clinical Assessment*

94 Participants for the current study were identified from the Zhongshan Angle Closure Prevention (ZAP)
95 Trial, a single-center randomized controlled trial based in Guangzhou, China.²⁴ Eligible participants aged
96 50 to 70 years with bilateral PACS received complete baseline eye examinations, including gonioscopy,
97 AS-OCT imaging, and ultrasound A-scan biometry, by trained ophthalmologists. PACS was defined as an
98 eye with two or more quadrants of angle closure, defined as inability to visualize pigmented TM based on
99 gonioscopy, in the absence of peripheral anterior synechiae (PAS), IOP greater than 21 mmHg, and
100 evidence of glaucomatous optic neuropathy or anterior segment ischemia from previous acute IOP increase.
101 Participants were re-examined at 2 weeks and 6, 18, 36, 54, and 72 months after baseline examination.
102 Study endpoints included incident PAC, defined as either: 1) IOP measurements above 24 mmHg on two
103 separate occasions; 2) development of at least one clock hour of PAS in any quadrant; or an acute attack of
104 angle closure.

105 Static gonioscopy was performed under dark ambient lighting standardized at less than 1 lux
106 illumination (EA30 EasyView Light Meter; Extech Instruments, Waltham, MA, USA) with a 1-mm light
107 beam and a Goldmann-type 1-mirror gonioscope (Haag-Streit AG, Koniz, Switzerland) prior to pupillary
108 dilation. Gonioscopy was performed by one of two fellowship-trained glaucoma specialists with high
109 intergrader agreement (weighted kappa > 0.80).²⁴ Care was taken to avoid light falling on the pupil,
110 inadvertent indentation of the globe, and tilting of the lens greater than 10 degrees. The angle was graded
111 in each quadrant according to the modified Shaffer classification system: grade 0, no structures visible;
112 grade 1, non-pigmented TM visible; grade 2; pigmented TM visible; grade 3, scleral spur visible; grade 4,
113 ciliary body visible. The cumulative gonioscopy score was the sum of gonioscopy grades from all 4
114 quadrants.

115 AS-OCT imaging was performed with the Visante AS-OCT system (Carl Zeiss Meditec, Inc.,
116 Dublin, CA, USA) under dark ambient lighting standardized at less than 1 lux illumination prior to pupillary
117 dilation. During imaging, eyelids were gently retracted taking care to avoid inadvertent pressure on the
118 globe. At the start of the ZAP Trial, only scans along the horizontal (temporal-nasal) meridian were
119 performed. Partway through the ZAP Trial, scans along the vertical (superior-inferior) meridian were also
120 performed. Ultrasound A-scan biometry (CineScan A/B, Quantel Medical, Bozeman, MT, USA) was
121 performed to measure axial length (AxL) and lens thickness (LT).

122 Only untreated eyes were included in the analysis in order to assess the natural progression of PACS
123 to PAC or AAC. Eyes that received laser peripheral iridotomy (LPI) were excluded from the study. Eyes
124 that were censored prior to the conclusion of the study due to incomplete follow-up or cataract surgery were
125 excluded from the primary analysis but were included in the sensitivity analysis.

126

127 *AS-OCT Image Analysis*

128 One AS-OCT image per eye oriented along the horizontal meridian or two images per eye oriented along
129 the horizontal and vertical meridians were analyzed using the custom Zhongshan Angle Assessment
130 Program, which automatically segmented anterior segment structures and produced biometric

131 measurements once the scleral spurs were marked.²⁵ Image analysis was performed by 5 certified graders
132 who were masked to examination results and intervention assignments. Graders confirmed the segmentation
133 and marked the scleral spurs in each image.²⁶

134 In total, 13 biometric parameters describing the anterior segment were measured in each AS-OCT
135 image.²⁷ Angle open distance (AOD) was defined as the perpendicular distance from the TM at 500
136 (AOD500) and 750 (AOD750) μm anterior to the scleral spur to the anterior iris surface, respectively.
137 Trabecular iris space area (TISA) was defined as the areas bounded anteriorly by AOD500 (TISA500) and
138 AOD750 (TISA750), respectively; posteriorly by a line drawn from the scleral spur perpendicular to the
139 plane of the inner scleral wall to the opposing iris; superiorly by the inner corneoscleral wall; and inferiorly
140 by the iris surface. Iris thickness at 750 (IT750) and 2000 (IT2000) μm from the scleral spur, iris area (IA),
141 iris curvature (IC), lens vault (LV), anterior chamber depth (ACD), anterior chamber width (ACW), anterior
142 chamber area (ACA), and pupillary diameter (PD) were also measured.^{27,28}

143 A set of 20 images from 20 eyes were randomly selected and graded independently by all 5 graders.
144 Inter-grader agreement in the form of intraclass correlation coefficients (ICC) ranged from good to excellent
145 for all AS-OCT parameters: AOD500 (0.83), AOD750 (0.82), TISA500 (0.90), TISA750 (0.88), IA (0.92),
146 IT750 (0.84), IT2000 (0.74), IC (0.90), ACD (0.99), PD (0.99), ACW (0.95), LV (0.91), ACA (0.99).²⁹

147

148 *Statistical Analysis*

149 Horizontal, vertical, and overall measurements of biometric parameters were calculated by averaging
150 corresponding measurements from horizontal, vertical, or both horizontal and vertical images, respectively.
151 Means and standard deviations were calculated for all continuous variables. Normality of data was assessed
152 using the Shapiro-Wilk test and by plotting histograms of measurement distributions. Means of continuous
153 variables were compared between progressors and non-progressors using the unpaired t-test. Proportions
154 of categorical variables were compared using the Pearson's chi-square test.

155 Univariable and multivariable logistic regression models were developed to assess the association
156 between baseline horizontal parameter measurements and progression. Vertical and overall parameter

157 measurements were excluded from these models due to weak differences between progressors and non-
158 progressors and number of missing vertical images. Multivariable model A was developed using the best
159 subset selection method to maximize the adjusted R^2 . This model was limited to 4 parameters due to the
160 relatively low number of cases of progression ($N = 34$). In multivariable model B, horizontal AOD500 was
161 replaced with cumulative gonioscopy score as a measure of angle width. Units for biometric parameters
162 were modified for physiologic significance and interpretability of odds ratios. In multivariable model C,
163 continuous measures of horizontal AOD500, horizontal IC, and age were replaced with categorical
164 measures: within or outside the lowest quartile of horizontal AOD500 measurements ($AOD500 < 0.042$
165 mm), lowest quartile of horizontal IC measurements ($IC < 0.335$ mm), and upper half of age ($age \geq 59$
166 years). In multivariable model D, the categorical measure of horizontal AOD500 was replaced with a
167 categorical measure of cumulative gonioscopy score: within or outside the lowest quartile of scores (score
168 < 3). Area under the receiver operating characteristic curve (AUC) metrics were calculated for models A
169 and C to assess predictive performance. A Cox proportional hazard model was developed with the same
170 parameters as multivariable model A but including eyes that were censored prior to the conclusion of the
171 study. This sensitivity analysis was performed to assess for biases associated with excluding these eyes
172 from the primary analysis. All analyses were performed using the R programming interface (version 4.0.3).
173 Statistical analyses were conducted using a significance level of 0.05.

174

175 **Results**

176 In total, 889 untreated eyes from 889 ZAP Trial participants received baseline clinical examinations. 225
177 eyes (25.3% of total) were excluded from the primary analysis due to being censored before the last (72-
178 month) visit. 21 eyes (2.4% of total) were excluded due to incomplete horizontal measurements, which
179 included 2 of the 36 untreated eyes that progressed from PACS to PAC or AAC.

180 643 untreated eyes of 643 participants were included in the current study. All 643 eyes had
181 horizontal images whereas 147 eyes (22.9% of included) were missing vertical images, which were not

182 collected until partway through the ZAP Trial. All AS-OCT images from these eyes had detectable scleral
183 spurs.

184 The mean age of participants included in the study was 58.7 ± 5.0 years (range 50-69 years). 116
185 participants (18.0%) were male and 527 participants (82.0%) were female, which was consistent with the
186 overall distribution of the ZAP Trial (17.0% male, 83.0% female).⁶ 34 of the 643 eyes (5.3%) progressed
187 from PACS to PAC or AAC, which was consistent with the overall rate of progression (5.4%) among
188 participants who completed the ZAP Trial. 29 of the 34 (85.3%) progressed due to PAS, and 8 of the 34
189 (23.5%) progressed due to elevated IOP (N = 4) or AAC (N = 4). The baseline mean modified Shaffer grade
190 was 0.89 ± 0.38 .

191 There were significant differences ($p < 0.05$) between progressors and non-progressors for 5
192 horizontal, 1 vertical, and 1 overall baseline AS-OCT biometric parameter/s. Progressors had significantly
193 smaller ($p < 0.05$) horizontal measurements of AOD500, AOD750, TISA500, IA, and IC, smaller vertical
194 measurements of TISA500, and smaller overall measurements of TISA500 (Table 1; Supplementary Table
195 1). Progressors also had higher IOP ($p = 0.03$) and greater LT ($p = 0.03$) at baseline. Difference in age
196 between progressors and non-progressors approached but did not reach statistical significance ($p = 0.051$).

197 On univariable logistic regression analysis, smaller horizontal measurements of AOD500 (OR =
198 1.14 per 0.01 mm decrease), AOD750 (OR = 1.07 per 0.01 mm decrease), TISA500 (OR = 1.41 per 0.01
199 μm^2 decrease), IA (OR = 1.20 per 0.1 mm^2 decrease), and IC (OR = 1.72 per 0.1 mm decrease) and higher
200 baseline IOP (OR = 1.14 per 1 mmHg increase) were significantly associated ($p < 0.05$) with greater odds
201 of progression (Table 2). In multivariable model A (AUC = 0.73), 3 out of 4 selected parameters were
202 significantly associated ($p < 0.03$) with progression (Table 2): older age (OR = 1.11 per year increase),
203 narrower horizontal AOD500 (OR = 1.10 per 0.01 mm decrease), and flatter horizontal IC (OR = 1.96 per
204 0.1 mm decrease). In multivariable model B, smaller cumulative gonioscopy score (OR = 1.03 per 1 grade
205 decrease; $p = 0.85$) was not associated with progression when replacing horizontal AOD500 (Table 3).

206 In multivariable model C (AUC = 0.72), the lowest quartile of horizontal AOD500 measurements
207 (OR = 3.10), lowest quartile of horizontal IC measurements (OR = 2.48), and upper half of ages (OR =

208 2.68) were significantly associated ($p < 0.02$) with increased odds of progression (Table 4). In multivariable
209 model D, the lowest quartile of cumulative gonioscopy scores was not associated with increased odds of
210 progression (OR = 1.51; $p = 0.32$), although the lowest quartile of horizontal IC measurements (OR = 3.08)
211 and upper half of ages (OR = 2.54) remained significantly associated ($p < 0.02$) with progression (Table 5).

212 Baseline demographics and biometric measurements were similar ($p > 0.15$) between participants
213 included (N = 643) in the primary analysis and participants excluded (N = 225) due to being censored before
214 the last (72-month) visit (Supplementary Table 2). The Cox proportional hazard model, which included all
215 censored eyes, produced results closely resembling multivariable model A (Supplementary Table 3). The
216 same three baseline parameters were significantly associated ($p < 0.03$) with progression, and their hazard
217 ratios closely approximated corresponding odds ratios from multivariable model A: older age (HR = 1.11
218 per year increase), narrower horizontal AOD500 (HR = 1.09 per 0.01 mm decrease), and flatter horizontal
219 IC (HR = 1.96 per 0.1 mm decrease).

220

221 Discussion

222 We assessed untreated eyes of ZAP participants and identified horizontal AOD500, horizontal IC, and age
223 as significant risk factors for progression from PACS to PAC or AAC over a 6-year period. Cumulative
224 gonioscopy score was not predictive of progression, providing evidence that OCT imaging of the anterior
225 segment may be a better tool than gonioscopy for determining risk of progression. AS-OCT measurements
226 of biometric parameters can help identify patients with early angle closure who are at higher risk of
227 progression to more severe disease.

228 A prevailing question in the field of glaucoma is which eyes with early angle closure (PACS) are
229 at higher risk of developing PACG and should be considered for treatment. Our results provide the first
230 evidence that patients with PACS and narrower baseline angle width measured by AS-OCT are at higher
231 risk of progression to PAC or AAC, which in turn increases risk of PACG. In multivariable model A, each
232 10 μm decrease in horizontal AOD500 increased odds of progression by approximately 10%. In terms of
233 per standard deviation decrease in horizontal AOD500, this translates to an odds ratio of 1.66. This finding

234 provides a quantitative framework for interpreting repeated measures of AOD500, such as longitudinal
235 changes in angle width over time or after treatment with LPI.³⁰ This finding is also consistent with previous
236 findings by Nongpiur et al. who reported that baseline AS-OCT measurements of angle width (AOD750)
237 are predictive of incident gonioscopic angle closure.³¹ Incident PAC and AAC are of greater clinical
238 significance compared to incident PACS, since both are more likely to lead to PACG. Nevertheless, our
239 findings in combination with previous findings together suggest that angle width measurements are
240 predictive of progression across the spectrum of primary angle closure disease (PACD).

241 Our results suggest that flatter baseline horizontal IC is a risk factor for progression, which is
242 surprising given that greater IC reflects increased pupillary block and is a well-established risk factor for
243 gonioscopic angle closure.³² One possible explanation for this finding is that eyes with non-pupillary block
244 mechanisms of angle closure, such as plateau iris or thick peripheral iris, are at higher risk for progression.
245 This could in part explain why LPI is not uniformly beneficial in all PACS eyes. An alternative explanation
246 is that eyes with less pupillary block at baseline have more capacity for worsening of pupillary block over
247 time, predisposing them to progression. Given that flatter IC was a significant risk factor for progression,
248 further study of this point is warranted. However, differentiating between these two explanations requires
249 modeling dynamic change-over-time parameters in addition to static parameters. Analysis of dynamic
250 parameters, while important, ultimately fell outside the scope of the current study, which focuses on
251 baseline factors that can help inform clinical decision making at initial diagnosis of PACS.

252 Older age remained a significant risk factor for progression from PACS to PAC or AAC even after
253 accounting for significant biometric covariates. Age likely serves as a surrogate for a wide range of static
254 biometric parameters that contribute to angle closure, such as ACD, LV, and LT.^{14,15,33,34} In addition, age
255 may also be associated with dynamic rates of change over time among biometric parameters.²¹ Based on
256 multivariable model A, each year of life increases the odds of progression by approximately 10%.
257 Therefore, the odds of progression is predicted to triple (OR = 2.83) per decade of life, which mirrors the
258 higher prevalence of PACG among elderly mainland and Singaporean Chinese.³⁵⁻³⁷ The importance of age
259 as a risk factor for progression highlights a potential limitation of the ZAP Trial cohort; the mean age of

260 participants at enrollment was 59.3 years, and participants over the age of 70 at baseline were excluded to
261 limit participant attrition and need for cataract surgery. Therefore, the low rate of progression observed in
262 the ZAP Trial may be at least partially attributable to the relatively young age of its participants and may
263 not generalize to patients over the age of 70.

264 Our results indicate that risk of progression is not equal among all PACS eyes, and that some PACS
265 eyes may benefit from prophylactic treatment. Multivariable model C provides a basic quantitative
266 framework to quantify risk conferred by individual parameters and identify patients at higher risk of
267 progression. High-risk features such as horizontal AOD500 < 0.042 mm, horizontal IC < 0.335 mm, and
268 age greater than 58 years confer higher risk of progression than their low-risk counterparts. Our model
269 predicts that patients 59 years of age and older with horizontal AOD500 < 0.042 mm have about 8 times
270 higher risk of progression, and patients with all three high-risk features have about 20 times higher odds.
271 The ZAP Trial reported that the number needed to treat to prevent one case of progression from PACS to
272 PAC was 44 eyes. It is intuitive that only treating a subset of high-risk PACS eyes would be associated with
273 a lower number needed to treat. However, more formal analyses and longitudinal studies are needed to
274 determine the exact benefit of using this approach to risk stratify and manage patients with PACS.

275 Horizontal measurements of multiple biometric parameters were associated with risk of
276 progression, but only TISA500 was associated in vertical scans. This finding suggests that not all sectoral
277 angle widths contribute equally to risk of progression. We speculate this is related to sectoral differences in
278 angle width; the superior sector of the angle tends to be the narrowest and the temporal and nasal sectors
279 tend to be widest.³⁸ Baseline angle narrowing in the superior sector is more common, which could explain
280 why biometric parameters describing this sector appear less useful for differentiating between progressors
281 and non-progressors. While there has been a recent trend toward analyzing more AS-OCT images per eye
282 to better represent sectoral variations among biometric parameters, the benefit of this approach appears to
283 be mitigated for predicting progression.^{38,39}

284 Continuous and categorical measures of cumulative gonioscopy score were not significantly
285 associated with progression, which highlights a limitation of gonioscopy in evaluating PACS eyes. Previous

286 studies demonstrated that AS-OCT measurements of angle width and gonioscopy grades are poorly
287 correlated in eyes with PACD.^{40,41} Other studies demonstrated that IOP and localized anatomical changes
288 are more strongly correlated with AS-OCT measurements of angle width than gonioscopy grades in subsets
289 of eyes with PACD.^{42,43} Our results suggest that AS-OCT measurements may provide a more clinically
290 useful measure of angle width than gonioscopy grades, at least for predicting progression from PACS to
291 PAC or AAC, and that disagreements between the two could reflect inherent limitations of gonioscopy for
292 evaluating eyes with PACD.

293 Our study has several limitations. First, it is important to acknowledge that multivariable model A
294 was only moderately predictive (AUC = 0.73) and cannot precisely identify eyes that will progress from
295 PACS to PAC or AAC. We averaged temporal and nasal measurements of biometric parameters to reduce
296 the total number of biometric parameters and avoid potential issues related to intra-eye measurement
297 correlations. We also excluded vertical and overall measurements from our multivariable models due to
298 weak differences between progressors and non-progressors and missing vertical images. It is conceivable
299 that data from individual sectors could provide additional information to predict progression. Therefore, a
300 more robust model utilizing all biometric parameters, perhaps developed using machine-learning methods,
301 may produce better predictive performance. Second, we did not have sufficient numbers of untreated eyes
302 that developed elevated IOP or AAC to perform sub-analyses on these more clinically significant
303 progression subtypes. Third, the number of progressors in our study was small (N = 34), which limited our
304 ability to develop more robust logistic regression models and detect weaker risk factors for progression.
305 Fourth, we worked with a definition of PAC that was narrower than its original epidemiological definition
306 (any PAS or IOP > 21 mmHg).³ This may limit the generalizability of our findings in clinical or research
307 settings where PACD is more broadly defined. Finally, all subjects in the ZAP Trial were Chinese and
308 between the ages of 50 to 70, which may limit the generalizability of our multivariable models for predicting
309 progression in other populations.

310 In conclusion, we assessed and modeled biometric risk factors for progression from PACS to PAC
311 in a mainland Chinese population. Our key finding is that AS-OCT measurements of angle width and IC

312 are predictive of progression whereas gonioscopy grades are not. These findings suggest that biometric
313 measurements could help risk stratify patients with early angle closure for disease progression. In addition,
314 eyecare providers may still consider treating some cases of PACS with LPI, especially those with high-risk
315 features (elderly patients with severe angle narrowing or iris flattening). However, further work is needed
316 to assess the clinical benefit of this approach in diverse populations and develop quantitative imaging-based
317 methods to identify treatable PACS and reduce the burden of PACG worldwide.

318

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438

439 Table Captions

440 **Table 1:** Differences among baseline demographics and horizontal (h) biometric measurements between
441 progressors and non-progressors.

442 **Table 2:** Univariable and multivariable logistic regression models of the association between progression
443 and continuous measures of clinical and biometric parameters.

444 **Table 3:** Multivariable logistic regression model with horizontal AOD500 replaced by cumulative
445 gonioscopy score.

446 **Table 4:** Univariable and multivariable logistic regression models of the association between progression
447 and categorical measures of horizontal AOD500 and IC and age.

448 **Table 5:** Univariable and multivariable logistic regression models of the association between progression
449 and categorical measures of cumulative gonioscopy score, horizontal IC, and age.

450

451 **Supplementary Table 1:** Differences among baseline demographics and vertical (v) and overall biometric
452 measurements between progressors and non-progressors.

453 **Supplementary Table 2:** Differences among baseline demographics and horizontal (h) biometric
454 measurements between participants included in the primary analysis and excluded due to being censored
455 before the last (72-month) visit.

456 **Supplementary Table 3:** Cox proportional hazard model of the association between progression and
457 parameters from multivariable model A, including eyes that were censored before the last (72-month) visit.

458

Table 1: Differences among baseline demographics and horizontal (h) biometric measurements between progressors and non-progressors.

Parameter	Units	Non-Progressors	Progressors	P-value *
		(N = 609)	(N = 34)	
		Mean (STD)	Mean (STD)	
Age	Years	58.567 (4.977)	60.294 (5.681)	0.051
Sex	Male/Female	110/499	6/28	1.000
IOP	mmHg	15.170 (2.873)	16.303 (2.974)	0.028
Gonioscopy score	mShaffer grade	3.584 (1.476)	3.296 (1.336)	0.265
hAOD500	mm	0.088 (0.053)	0.057 (0.050)	0.001
hAOD750	mm	0.127 (0.062)	0.102 (0.066)	0.028
hTISA500	mm ²	0.055 (0.034)	0.033 (0.021)	<0.001
hTISA750	mm ²	0.103 (0.071)	0.092 (0.086)	0.381
hIA	mm ²	1.606 (0.216)	1.526 (0.145)	0.045
hIT750	mm	0.495 (0.067)	0.485 (0.071)	0.431
hIT2000	mm	0.616 (0.081)	0.602 (0.088)	0.319
hIC	mm	0.391 (0.088)	0.351 (0.089)	0.016
hACD	mm	2.217 (0.198)	2.162 (0.239)	0.144
hPD	mm	4.410 (0.702)	4.477 (0.731)	0.611
hACW	mm	11.520 (0.396)	11.505 (0.399)	0.837
hLV	mm	0.708 (0.241)	0.718 (0.277)	0.829
hACA	mm ²	15.774 (2.008)	15.382 (2.422)	0.303
LT	mm	4.871 (0.297)	4.956 (0.405)	0.113
AXL	mm	22.518 (0.719)	22.381 (0.701)	0.278

Abbreviations: h: Horizontal. IOP: Intraocular Pressure. AOD500/750: Angle Opening Distance 500/750 μm from the scleral spur. TISA500/750: Trabecular-Iris Space Area 500/750 μm from the scleral spur. IA: Iris Area. IT750/2000: Iris Thickness 750/2000 μm from the scleral spur. IC: Iris Curvature. ACD: Anterior Chamber Depth. PD: Pupillary Diameter. ACW: Anterior Chamber Width. LV: Lens Vault. ACA: Anterior Chamber Area. LT: Lens Thickness. AXL: Axial Length.

* P-values calculated using unpaired t-test.

Boldface indicated significant at $P < 0.05$.

Table 2: Univariable and multivariable logistic regression models of the association between progression and continuous measures of clinical and biometric parameters.

Parameter	Interval	Univariable		Multivariable Model A	
		OR (95% CI)	P-value	OR (95% CI)	P-value
Sex	Female	1.03 (0.44-2.80)	0.951		
Age	1 year	1.07 (1.00-1.15)	0.053	1.11 (1.03-1.20)	0.007
IOP	1 mmHg	1.14 (1.01-1.28)	0.029		
Gonioscopy score	1 mShaffer grade	0.88 (0.69-1.11)	0.265		
hAOD500	0.01 mm	0.88 (0.81-0.95)	0.001	0.91 (0.84-0.99)	0.027
hAOD750	0.01 mm	0.93 (0.88-0.99)	0.029		
hTISA500	0.01 mm ²	0.71 (0.54-0.91)	0.011		
hTISA750	0.01 mm ²	0.98 (0.89-1.04)	0.574		
hIA	0.1 mm ²	0.83 (0.68-0.99)	0.046		
hIT750	0.1 mm	0.80 (0.46-1.39)	0.43		
hIT2000	0.1 mm	0.80 (0.52-1.23)	0.318		
hIC	0.1 mm	0.58 (0.36-0.89)	0.016	0.51 (0.31-0.84)	0.010
hACD	0.1 mm	0.87 (0.72-1.05)	0.145	0.87 (0.71-1.06)	0.162
hPD	mm	1.15 (0.68-1.96)	0.611		
hACW	mm	0.99 (0.90-1.09)	0.837		
hLV	0.1 mm	1.02 (0.88-1.18)	0.829		
hACA	mm ²	0.91 (0.76-1.09)	0.302		
LT	0.1 mm	1.10 (0.98-1.24)	0.11		
AXL	mm	0.76 (0.47-1.24)	0.277		

Abbreviations: h: Horizontal. IOP: Intraocular Pressure. AOD500/750: Angle Opening Distance 500/750 μm from the scleral spur. TISA500/750: Trabecular-Iris Space Area 500/750 μm from the scleral spur. IA: Iris Area. IT750/2000: Iris Thickness 750/2000 μm from the scleral spur. IC: Iris Curvature. ACD: Anterior Chamber Depth. PD: Pupillary Diameter. ACW: Anterior Chamber Width. LV: Lens Vault. ACA: Anterior Chamber Area. LT: Lens Thickness. AXL: Axial Length.

Boldface indicated significant at $P < 0.05$.

Table 3: Multivariable logistic regression model with horizontal AOD500 replaced by cumulative gonioscopy score.

Parameter	Interval	Multivariable Model B	
		OR (95% CI)	P-value
Age	1 year	1.11 (1.03-1.20)	0.006
Gonioscopy score	1 mShaffer grade	0.94 (0.73-1.22)	0.665
hIC	0.1 mm	0.45 (0.27-0.72)	0.001
hACD	0.1 mm	0.82 (0.67-1.00)	0.056

Abbreviations. hIC: Horizontal Iris Curvature. hACD: Horizontal Anterior Chamber Depth.

Boldface indicated significant at $P < 0.05$.

Table 4: Univariable and multivariable logistic regression models of the association between progression and categorical measures of horizontal AOD500 and IC and age.

Parameter	Interval	Progressors (N)	Univariable		Multivariable Model C	
			OR (95% CI)	P-value	OR (95% CI)	P-value
hAOD500	≥ 0.042 mm	20	-	-	-	-
	< 0.042 mm	14	2.67 (1.30-5.38)	0.006	3.10 (1.49-6.37)	0.002
hIC	≥ 0.34 mm	19	-	-	-	-
	< 0.34 mm	15	2.24 (1.08-4.52)	0.026	2.48 (1.18-5.10)	0.014
Age	< 59 years	11	-	-	-	-
	≥ 59 years	23	2.33 (1.14-5.05)	0.024	2.68 (1.29-5.90)	0.01

Abbreviations: hAOD500: Horizontal Angle Opening Distance 500 µm from the scleral spur. hIC: Horizontal Iris Curvature.

Boldface indicated significant at $P < 0.05$.

Table 5: Univariable and multivariable logistic regression models of the association between progression and categorical measures of cumulative gonioscopy score, horizontal IC, and age.

Parameter	Interval	Progressors (N)	Univariable		Multivariable Model D	
			OR (95% CI)	P-value	OR (95% CI)	P-value
Gonioscopy score	≥ 3 mShaffer grade	25	-	-	-	-
	< 3 mShaffer grade	9	1.26 (0.55-2.680)	0.559	1.51 (0.64-3.29)	0.32
hIC	≥ 0.34 mm	19	-	-	-	-
	< 0.34 mm	15	2.67 (1.30-5.38)	0.006	3.08 (1.48-6.34)	0.002
Age	< 59 years	11	-	-	-	-
	≥ 59 years	23	2.33 (1.14-5.05)	0.024	2.54 (1.23-5.55)	0.014

Abbreviations. hIC: Horizontal Iris Curvature.

Boldface indicated significant at $P < 0.05$.



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TITLE OF ARTICLE: **Ocular Biometric Risk Factors for Progression of Primary Angle Closure Disease: The Zhongshan**

Angle Closure Prevention Trial

AUTHORS:

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OTHER CONTRIBUTIONS:

Précis

Angle width and iris curvature predict progression of primary angle closure suspects to primary angle closure and acute angle closure. Ocular biometric measurements help risk stratify patients with early angle closure for more severe disease.

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