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Development of angle closure and associated risk factors: The Handan eye study

Ye Zhang,[1] Qing Zhang,[2] Ravi Thomas,[3,4] Si Zhen Li[5] and Ning Li Wang[1,2]

[1]Beijing Tongren Eye Center, Beijing Key Laboratory of Ophthalmology and Visual Science, Beijing Tongren Hospital, Capital Medical University, Beijing, China
[2]Beijing Institute of Ophthalmology, Beijing, China
[3]Queensland Eye Institute, Brisbane, Australia
[4]University of Queensland, Brisbane, Australia
[5]Nanjing Tongren Hospital, Jiangsu, China

ABSTRACT.

Purpose: **To investigate the development of angle closure from baseline open angle and associated risk factors in a rural Chinese population through a longitudinal study over a 5-year period.**

Methods: **Subjects aged ≥30 years and older with bilateral open angles at baseline of the Handan Eye Study who participated in the follow-up and had undergone both baseline and follow-up gonioscopic examinations were included. Subjects with any form of angle closure, glaucoma, incisional ocular surgery or other conditions that could influence the results were excluded. The development of angle closure was defined as the presence of primary angle closure suspect (PACS) or primary angle closure (PAC)/primary angle closure glaucoma (PACG) during the follow-up in normal subjects with baseline bilateral open angles. Logistic regression was performed to identify the baseline risk factors for the development of angle closure.**

Results: **A total of 457 subjects with bilateral open angles at baseline aged 53.0 (45.5, 58.0) years were enrolled. 94.7% of the included cases developed PACS, 5.3% developed PAC and no one developed PACG after 5 years. In logistic regression, significant risk factors for the development of angle closure were shallower central anterior chamber depth (ACD) ($p = 0.002$) and narrower mean angle width ($p < 0.001$).**

Conclusions: **This study reports the development from baseline open angle to angle closure after a 5-year follow-up. We confirm that the mean angle width and central ACD were independent predictive risk factors for the development of any form of angle closure.**

Key words: development of angle closure – primary angle closure suspect – primary angle closure – primary angle closure glaucoma – risk factors

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Introduction

Glaucoma has long been recognized as a major cause of ocular morbidity and the leading cause of irreversible blindness worldwide (Foster et al. 2001; Quigley et al. 2006). One of the major types of glaucoma, primary angle closure glaucoma (PACG), is an aggressive condition which can lead to severe vision loss and has the highest prevalence among Asian populations, especially Chinese (Foster et al. 2001; Quigley et al. 2006; Tham et al. 2014). With 10 million people estimated to be affected with PACG in China by 2020 (about half of the total worldwide), the disease is a serious challenge for health care in China (Foster et al. 2001).

Primary angle closure disease (PACD) is considered to be a potentially preventable disease. If detected and treated with prophylactic intervention in the PACS and early PAC stages, the progression to PACG can be prevented to some extent or slowed (Nongpiur et al., 2011b; Sun et al. 2017). However, there is a paucity of information about the risk factors associated with the development of angle closure in those who initially have open angles (Tham et al. 2014; Sun et al. 2017).

According to previous studies, shallower limbal ACD, shallower central ACD, rapid shallowing of the ACD, increased lens thickness (LT), shorter axial length, anteriorly positioned lens, hyperopia, higher intraocular pressure

(IOP) and narrower anterior chamber angle have been reported to be associated with the development of angle closure in different populations (Alsbirk et al. 1992; Ye et al. 1998; Yip et al. 2008; George et al. 2012; Kashiwagi et al. 2013; Vijaya et al. 2013; Wang et al. 2019). No studies referring to the rural Chinese population were reported.

The aim of this study was to report the associated risk factors for the development of angle closure from baseline bilateral open angles in a rural Chinese population.

Methods

Subjects

The Handan Eye Study (HES) was a population-based cohort study conducted on a sample of rural Chinese adults initiated in 2006. At the baseline, 6830 eligible subjects aged 30 years or older were included from 13 villages in Yongnian County, Handan City, Hebei Province, Northern China, using a clustered random sampling method (Liang et al. 2009). The follow-up research was implemented between 2012 and 2013, following the same protocol. All participants from the baseline study were invited to take part in follow-up examinations 5 years later. This follow-up study included 5394 participants who returned for the repeat examinations (85.3% of survivors).

The subjects enrolled in our study were participants who received gonioscopic examinations at both baseline and follow-up and were diagnosed with baseline bilateral open angles. Those who satisfied the following criteria were excluded: subjects who were diagnosed with any form of angle closure, primary open angle glaucoma (POAG) or any form of secondary glaucoma, leucoma, keratoconus, iridocyclitis, iris or ciliary body cysts or tumours, spherophakia, congenital microphthalmia etc., had incisional ocular surgery or ocular trauma, which could have influenced the results at the baseline examination. Subjects who had bilateral cataract surgery during the 5-year follow-up (if it was unilateral cataract surgery, untreated eyes were used for outcome analysis) were also excluded from the analysis.

This study was conducted in accordance with the Helsinki Declaration and was approved by the Ethics Committee of Beijing Tongren Hospital. The subjects were adequately informed of the study, and verbal and written informed consent was obtained from all of them.

Examination

The ophthalmic examination consisted of measuring the presenting visual acuity (PVA) and best-corrected visual acuity (BCVA) using logarithm of minimum angle of resolution (logMAR) 4-metre charts, objective and subjective refraction, slit-lamp biomicroscopy, visual field examination, intraocular pressure (IOP) measurement, gonioscopy, A-scan ultrasound biometry and fundus examination.

Refraction and corneal curvature radius (CCR) were measured using a KR-8800 auto kerato-refractometer (Topcon, Tokyo, Japan), visual field test using the standard 24-2 Swedish Interactive Testing Algorithm (SITA) program on a visual field analyser (Humphrey Visual Field Analyzer 740i or 750i; Carl Zeiss, Jena, Germany). Slit-lamp biomicroscopy was performed, and peripheral anterior chamber depth was graded according to the modified van Herick system, in which the limbal chamber depth was graded as a percentage fraction of the thickness of the adjacent cornea at the most peripheral point in the following seven categories: 0%, 5%, 15%, 25%, 40%, 75% and ≥100% (Foster et al. 2000). Intraocular pressure (IOP) was recorded using a Kowa applanation tonometer (HA-2, Kowa Company Ltd. Tokyo, Japan) under topical anaesthesia using proparacaine 0.5% and fluorescein staining of the tear film. The right eye was measured first, and 2 measurements of IOP were taken per eye; if they differed by more than 2 mmHg, a third measurement was taken. The mean value of two measurements with smaller differences was identified as the IOP value.

Gonioscopy was performed on one in ten participants as well as on all persons with limbal anterior chamber depth (LACD) ≤40%, IOP >21 mmHg, and those having a history of glaucoma or suspect, with a one-mirror Goldmann gonioscopic lens (Ocular Instruments, Bellevue, WA) at ×25 magnification by experienced ophthalmologists at baseline and follow-up. The gonioscopic observations were standardized. The baseline gonioscopic examinations were performed by a single observer. The follow-up gonioscopic examinations were performed by one of two observers who had a weighted kappa score of 0.76. Static examination was performed in dim ambient illumination with a shortened slit that did not fall on the pupil. The anterior chamber angle width was graded according to the Spaeth system and recorded as 0, 10, 20, 30, 40 and 50 degrees (°), and the peripheral iris contour, degree of trabecular meshwork pigmentation and other angle abnormalities were recorded in all four quadrants of each eye. The mean angle width was calculated as the mean value of the angle widths in four quadrants. Indentation gonioscopy was performed with increased illumination after static gonioscopy, to assess angle opening, and findings on indentation were recorded.

A-scan ultrasound was performed by a 10-MHz A/B-mode ultrasound device (CineScan; Quantel Medical, Clermont-Ferrand, France), using a hard-tipped, corneal contact probe mounted on a slit lamp at baseline and an OcuScan RxP (Alcon, Inc., Fort Worth, TX, USA) at the follow-up. The anterior chamber depth (ACD), lens thickness (LT) and axial length (AL) were measured before mydriasis. Absolute lens position (ALP) was defined as ACD + 1/2 × LT and relative lens position (RLP) as ALP/AL.

All subjects except those with a broad peripheral anterior synechiae (PAS) on gonioscopy (≥6 clock hours) who have a high risk of acute angle closure (AAC) underwent pupillary dilation using 1% tropicamide. Lens grading for cataract using the lens opacity classification system III (LOCS III) was performed, comparing with standard photographs for nuclear opalescence (NO), nuclear colour (NC), cortical cataract (CC) and posterior subcapsular cataract (PSC), after pupil dilation by two trained graders in baseline and follow-up examinations (Chylack et al. 1993). The NO scores (ranged from 0.1 to 6.9 with one decimal) and CC scores (ranged from 0.1 to 5.9 with one decimal) were used in our study to evaluate the severity of cataract.

Stereoscopic evaluation of the optic nerve head was performed using a +78 diopter lens or +90 diopter lens at ×16 magnification after pupil dilation and the slit lamp. The vertical and

horizontal cup-to-disc ratios (CDRs) were measured and recorded. The presence of any notching, splinter haemorrhages or peripapillary atrophy was documented.

All participants underwent height, weight, waist circumference and hip circumference measurements. Body mass index (BMI) and waist hip ratio (WHR) were calculated for all participants. We also administered questionnaires for assessing the socioeconomic status, education level, demographic and personal history (smoking, alcohol consumption and diet), and any history of ophthalmic problems or surgeries, systemic diseases such as diabetes mellitus, hypertension, use of systemic or topical medication were also elicited and recorded.

Definition of primary angle closure disease

The definitions developed by the International Society for Geographical and Epidemiological Ophthalmology (ISGEO) were used for the states of PACD in our study: PACS: an eye in which 180° or more of the posterior pigmented trabecular meshwork could not be seen during a static examination, with IOP <21 mmHg and no PAS, previous AAC or glaucomatous optic neuropathy (GON) (Foster et al. 2002). PAC/PACG: a PACS eye with established PAS and/or IOP >21 mmHg and/or GON (Foster et al. 2002).

The development of angle closure in this study was defined as the presence of PACS (occludable angle on gonioscopy) or PAC/PACG (the presence of increased IOP and/or the presence of PAS in PACS subjects with or without GON) during the follow-up in normal subjects with bilateral open angles at baseline.

Statistical analysis

All statistical analyses were performed using SPSS statistical software (Version 25.0; SPSS, Inc., Chicago, IL, USA). We used ocular factors of the right eye for cases where either both eyes and the right eye only developed angle closure. For those with development of angle closure only in the left eye, ocular factors of the left eye were used.

Comparison of variables between subjects with developed angle closure and controls was done using the independent *t*-test (for variables demonstrating a normal distribution) or Mann–Whitney *U*-test (for variables failing to demonstrate a normal distribution) for continuous variables and Pearson's chi-square test for categorical variables. Statistical significance was assessed at p values less than 0.05.

Univariate and multivariate logistic regression was performed to identify the baseline risk factors for the development of any angle closure; these included age, sex, IOP, biometric parameters, BMI, socioeconomic status, education level, demographic and personal history. Variables with a p value less than 0.05 in the univariate logistic regression were included in the multivariate regression analysis.

Receiver operating characteristic (ROC) curves and area under the curve (AUC) were used as an index of testing the performance of baseline ocular parameters on predictive detecting development of any forms of angle closure.

Results

The number of participants who received gonioscopic examination in the baseline study was 2046. Of these, 376 were not eligible for the follow-up study because (1) died, 153 subjects (7.48%), (2) had severe physical or mental diseases, 48 subjects (2.35%), (3) were at work, 103 subjects (5.03%), (4) refused to attend, 54 subjects (2.64%), (5) were out of contact, 18 subjects (0.88%), leaving 1670 participants who completed the follow-up study. Among them, 16 refused or could not tolerate gonioscopic examination. 552 did not meet the requirements for gonioscopic examination in the follow-up study. Hence, a total of 1102 participants received gonioscopic examinations in both baseline and in the follow-up study (Fig.).

In comparison with non-examinees, the enrolled examinees tended to be older ($p < 0.001$); female ($p < 0.001$); have lower income ($p < 0.001$); likely to be hypertensive ($p = 0.006$); and have larger SE ($p < 0.001$), smaller ACD ($p < 0.001$), larger LT ($p < 0.001$) and smaller AL ($p < 0.001$) (Table 1). No difference was noted in education level, prevalence of diabetes, prior cataract surgery, BMI and IOP.

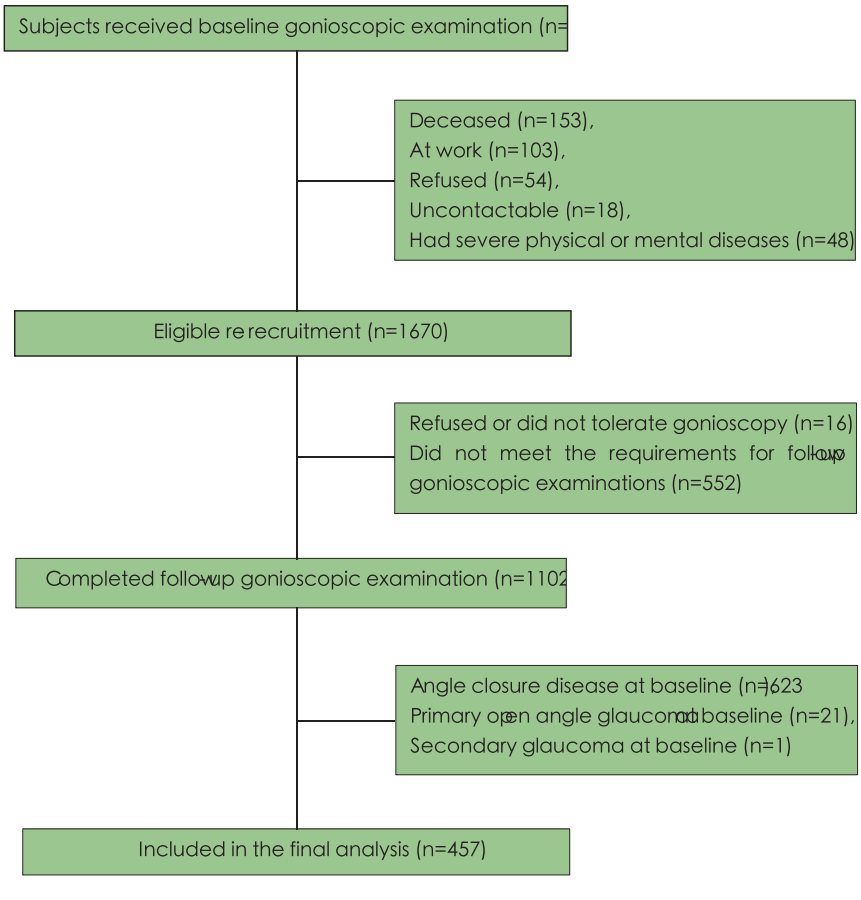

Fig. 1. Flow chart showing the enrolment of subjects

Among the 1102 subjects who completed the baseline and follow-up gonioscopic examinations, 623 subjects presented with PACD, 21 with POAG and 1 with secondary glaucoma at baseline. Three subjects received bilateral cataract surgery during the five-year period, including 2 with PACD and 1 with POAG at baseline. Eight subjects with unilateral cataract surgery (4 in the left eye and 4 in the right eye) during the 5 years were included, and the eyes on which the cataract surgery was not performed were analysed. A total of 457 subjects with bilateral open angles at baseline aged 53.0 (45.5, 58.0) years who had sufficient data were enrolled in the study (Fig. 1). 160 were male, and 297 were female. The overall development of any form of angle closure disease was 150 cases.

Eighty-one cases developed unilateral angle closure (33 involved the right eye and 48 involved the left eye), and 69 cases developed bilateral angle closure. Primary angle closure suspect (PACS) was the most common form of angle closure to develop, with 142 of 150 cases (94.7%) being classified as PACS. Eight of 150 cases (5.3%) developed PAC in either eye, and none developed PACG. All the 8 cases with PAC were unilateral and presented with PAS, but not an elevated IOP.

Compared with those who did not develop any form of angle closure over the 5-year period, those who developed angle closure were more likely to be female ($p = 0.016$), had shallower limbal ACD ($p = 0.040$) and central ACD ($p < 0.001$), had narrower mean angle width ($p < 0.001$), had thicker lenses ($p = 0.005$), had smaller ALP ($p < 0.001$) and smaller RLP ($p = 0.004$), and had shorter AL ($p < 0.001$) at baseline (Table 2). No difference was found in age, education level, income, prevalence of hypertension, prevalence of diabetes, BMI, WHR, cataract surgery, SE, CCR, IOP, NO score and CC score.

In multivariate logistic regression, significant risk factors for the development of any form of angle closure were shallower central ACD ($p = 0.003$) and narrower mean angle width ($p < 0.001$) (Table 3).

ROC analysis was used to assess the potential performance of mean angle width and central ACD as a combined determinant of development of any form of angle closure (Fig. 2). The AUC was 0.703 (95% CI, 0.650–0.753).

Table 1. Baseline characteristics of subjects who did and did not receive follow-up gonioscopic examinations

Parameter	Non-Examinees (n = 568)	Examinees (n = 1102)	p value
Age (IR), years	52.0 (41.0, 59.0)	56.0 (50.0, 61.0)	<0.001†
Gender			
Male (%)	265 (46.7)	300 (27.2)	<0.001‡
Female (%)	303 (53.3)	802 (72.8)	
Education			
None (%)	92 (16.2)	219 (19.9)	0.068‡
Yes (%)	476 (83.8)	883 (80.1)	
Income			
<1800	191 (33.6)	525 (47.6)	<0.001‡
≥1800	276 (48.6)	392 (35.6)	
Hypertension			
No (%)	278 (48.9)	461 (41.8)	0.006‡
Yes (%)	290 (51.1)	641 (58.2)	
Diabetes			
No (%)	528 (93.0)	1022 (92.7)	0.871‡
Yes (%)	40 (7.0)	80 (7.3)	
BMI (IR), kg/m^2	24.45 (22.22, 26.44)	24.28 (22.22, 26.67)	0.899†
Prior cataract surgery			
No (%)	549 (96.7)	1101 (99.9)	0.077‡
Yes (%)	3 (0.5)	1 (0.1)	
SE (IR), diopter	−0.25 (−0.75, 0.75)	0.50 (−0.25, 1.25)	<0.001†
IOP (IR), mmHg	15.3 (13.3, 17.5)	15.3 (13.3, 17.3)	0.576†
Central ACD (IR), mm	2.81 (2.50, 3.07)	2.45 (2.18, 2.70)	<0.001†
LT (IR), mm	4.66 (4.35, 4.96)	4.87 (4.62, 5.17)	<0.001†
AL (IR), mm	22.86 (22.36, 23.34)	22.38 (21.90, 22.86)	<0.001†

ACD = anterior chamber depth, AL = axial length, BMI = body mass index, IOP = intraocular pressure, IR = interquartile range, LT = lens thickness, SD = standard deviation, SE = spherical equivalent.
* Independent t-test.
† Mann–Whitney U-test.
‡ Chi-square test.

Discussion

This study on the development of angle closure from baseline normal subjects with open angle was based on the 5-year follow-up of a cohort of subjects who participated in the Handan Eye Study. Since not all the subjects at baseline and follow-up received gonioscopic examinations, we were not able to provide the incidence of angle closure. We could, however, provide data on the progression of angle closure from baseline, the demographic and biometric characteristics of subjects who developed angle closure compared with those who did not, as well as explore associations between pre-existing risk factors at baseline and the development of any form of angle closure. There were no cases of AAC; all subjects with progression developed either PACS or PAC.

Previous cross-sectional studies have shown that the prevalence of eyes with angle closure is high among the elderly and women, which we found in the baseline study of the HES (Yamamoto et al. 2005; Casson et al. 2009; Liang et al. 2011). Our study suggested that female subjects with bilateral open angles at baseline were more likely to develop angle closure compared with those who did not, but no statistically significant difference in age was found between the two groups. We did find that the progression from open angle to angle closure peaked in those in their 50s.

Ocular biometric parameters are known risk factors for PACD. Eyes with angle closure tended to have shallower ACD, narrower angle width, more hyperopic spherical equivalence, thicker lens, greater lens vault and shorter AL than the eyes of those without angle closure (George et al. 2003; Lavanya et al. 2008; Casson et al. 2009; Nongpiur et al., 2011a). Shorter AL, shallower ACD and narrower angle recess width are all associated with a crowded anterior segment which makes the eye susceptible to PACD

Table 2. Demographic and biometric characteristics of subjects with baseline open angles who did and did not develop angle closure

Parameter	Subjects who developed angle closure (n = 150)	Subjects who did not develop angle closure (n = 307)	p value
Age (IR), years	53.0 (48.0, 58.0)	52.0 (42.0, 58.0)	0.203†
Female (%)	109 (72.7)	188 (61.2)	0.016‡
Education, none (%)	17 (11.3)	38 (12.4)	0.747‡
Low income, < ¥1800/year (%)	64 (42.7)	110 (35.8)	0.062‡
Hypertension, present (%)	80 (53.3)	152 (49.5)	0.443‡
Diabetes, present (%)	10 (6.7)	18 (5.9)	0.804‡
BMI (IR), kg/m^2	24.56 (22.31, 26.78)	24.35 (22.31, 26.78)	0.606†
WHR (IR)	0.90 (0.88, 0.94)	0.90 (0.87, 0.93)	0.140†
Cataract surgery (%)	0 (0.0)	4 (1.3)	0.160‡
SE (IR), diopter	0.31 (−0.38, 0.75)	0.13 (−0.50, 0.75)	0.288†
CCR (Mean ± SD), mm	7.62 ± 0.25	7.64 ± 0.26	0.330*
IOP (IR), mmHg	15.5 (13.5, 17.8)	15.5 (13.5, 17.3)	0.171†
Limbal ACD, ≤ 40% (%)	91 (60.7)	155 (50.5)	0.040‡
Mean angle width (IR), °	27.5 (25.0, 30.0)	30.0 (25.0, 35.0)	<0.001†
Central ACD (IR), mm	2.57 (2.31, 2.77)	2.73 (2.46, 2.97)	<0.001†
LT (IR), mm	4.75 (4.57, 5.07)	4.67 (4.41, 5.01)	0.005†
ALP (IR), mm	4.93 (4.76, 5.11)	5.05 (4.87, 5.25)	<0.001†
RLP (IR)	0.22 (0.21, 0.23)	0.22 (0.22, 0.23)	0.004†
AL (Mean ± SD), mm	22.47 ± 0.67	22.72 ± 0.71	<0.001*
NO score (IR)	2.0 (1.4, 2.5)	2.0 (1.4, 2.5)	0.333†
CC score (IR)	0.1 (0.1, 0.5)	0.1 (0.1, 0.5)	0.505†

ACD = anterior chamber depth, AL = axial length, ALP = absolute lens position, BMI = body mass index, CC = cortical cataract, CCR = corneal curvature radius, IOP = intraocular pressure, IR = interquartile range, LT = lens thickness, NO = nuclear opalescence, RLP = relative lens position, SD = standard deviation, SE = spherical equivalent, WHR = waist hip ratio.
* Independent t-test.
† Mann–Whitney U-test.
‡ Chi-square test.

(Vijaya et al. 2013). Hyperopia is a known risk factor; this could be due to two possible reasons. First, eyes with hyperopia tend to have shorter AL and crowed anterior segment which makes these eyes susceptible to angle closure (Vijaya et al. 2013). Second, hyperopia may be caused by cortical cataracts which increase the lens thickness and contribute to angle closure (Wong et al. 2001; Vijaya et al. 2013). The lens is believed to play a crucial role in the pathogenesis of PACD because of increased lens thickness and/or a more anterior position (Vijaya et al. 2013). However, the exact association between lens and angle closure is equivocal and inconsistent (Yamamoto et al. 2005; Casson et al. 2009; Liang et al. 2011; Nongpiur et al., 2011a; Vijaya et al. 2013). One possible explanation for that is the inability to control the accommodation while measuring the lens thickness (George et al. 2012).

We found that compared with those who did not develop angle closure after 5-year of follow-up, subjects who developed angle closure from baseline open angle tended to be female, had shallower central ACD and limbal ACD, narrower anterior angle width,

Table 3. Factors associated with the development of any form of angle closure in the Handan Eye Study

	Univariate logistic regression		Multivariate logistic regression			
Variable	OR (95% CI)	p value	Estimated Regression Coefficient	Chi-square	OR (95% CI)	p value
Age	1.016 (0.995, 1.037)	0.130				
Female	1.683 (1.099, 2.577)	0.017	-	-	-	-
Family history of glaucoma	1.238 (0.441, 3.475)	0.685				
Education, none	0.905 (0.492, 1.663)	0.747				
Low income, <¥1800/year	1.511 (0.979, 2.331)	0.062				
Hypertension, present	1.165 (0.788, 1.723)	0.443				
Diabetes, present	1.107 (0.497, 2.466)	0.804				
BMI	1.011 (0.952, 1.074)	0.720				
WHR	1.237 (0.196, 7.798)	0.821				
SE	1.205 (0.921, 1.577)	0.174				
CCR	0.678 (0.311, 1.480)	0.329				
IOP	1.046 (0.981, 1.115)	0.170				
Limbal ACD, ≤40%	1.513 (1.017, 2.249)	0.041	-	-	-	-
Mean angle width	0.911 (0.878, 0.945)	<0.001	−0.075	14.117	0.927 (0.892, 0.965)	<0.001
Central ACD	0.274 (0.157, 0.481)	<0.001	−2.210	8.694	0.110 (0.025, 0.477)	0.003
LT	1.690 (1.068, 2.673)	0.025	−0.791	3.048	0.454 (0.187, 1.102)	0.081
ALP	0.226 (0.109, 0.469)	<0.001	-	-	-	-
RLP	< 0.001 (<0.001, 0.014)	0.014	30.192	2.897	1.295E+13 (0.010, 1.631E+28)	0.089
AL	0.596 (0.442, 0.804)	0.001	-	-	-	-
NO score	1.180 (0.949, 1.468)	0.137	-	-	-	-
CC score	0.990 (0.802, 1.222)	0.925	-	-	-	-

ACD = anterior chamber depth, AL = axial length, ALP = absolute lens position, BMI = body mass index, CC = cortical cataract, CCR = corneal curvature radius, CI = confidence interval, IOP = intraocular pressure, LT = lens thickness, NO = nuclear opalescence, OR = odds ratio, RLP = relative lens position, SE = spherical equivalent, WHR = waist hip ratio.

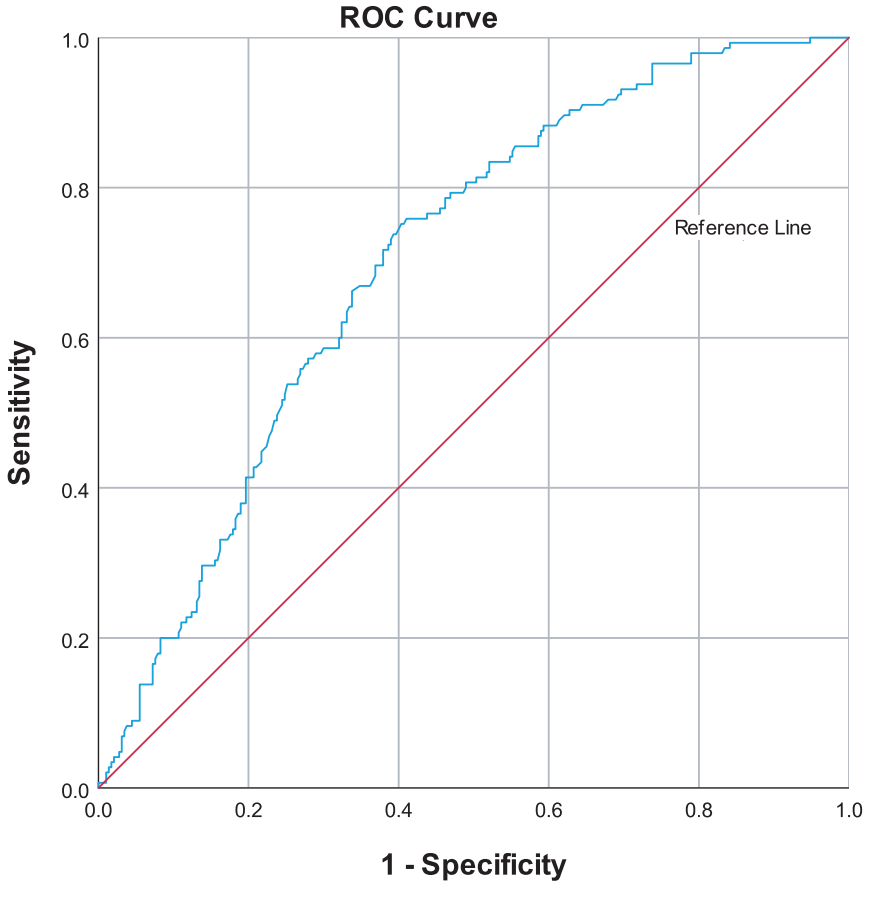

Fig. 2. The receiver operating characteristics curve of mean angle width and central anterior chamber depth as a combined determinant of development of primary angle closure

thicker lens, smaller ALP and RLP and shorter axial length. We further observed that the mean angle width and central ACD were determinants for the development of angle closure. However, these two parameters as a combined determinant had an AUC of 0.703, not enough predictive ability in deciding who will develop angle closure in open angle subjects.

To date, only a few prospective studies conducted on Eskimos, Chinese, Caucasian, Indians, Mongolians or Japanese have reported the progression from open angle to angle closure and the associated risk factors, as summarized in Table 4 (Alsbirk et al. 1992; Wilensky et al. 1993; Erie et al. 1997; Ye et al. 1998; Yip et al. 2008; Kashiwagi et al. 2013; Vijaya et al. 2013; Wang et al. 2019).

Although the rates of development of angle closure differed among these studies which may be caused by different inclusion criteria and populations, the important common risk factors which have consistently been shown to be associated with the development of angle closure in longitudinal studies were shallower ACD and narrower anterior chamber angle and this was also the case in our study (Alsbirk et al. 1992; Ye et al. 1998; Thomas et al. 2003a; Thomas et al. 2003b; Yip et al. 2008; George et al. 2012; Kashiwagi et al. 2013; Vijaya et al. 2013; Wang et al. 2019).

However, we found that the combined determinant of central ACD and mean angle width did not have strong enough predictive ability to warrant its use in determining who requires more intensive monitoring for the development of angle closure. The possible reason might be that other dynamic risk factors involved in the pathogenesis of PACD were not included, such as dynamic iris changes with pupil dilation (Zhang et al. 2014; Zhang et al. 2015; Zhang et al. 2016).

In our previous studies, we reported an AUC of 0.844 with inclusion of angle recess area at 750 μm, anterior chamber volume, lens vault and iris cross-sectional area change / pupil diameter change after physiologic mydriasis in the prediction model for detection of PACS (Zhang et al. 2020). In the future study, we tend to investigate the demographic, ocular anatomical and dynamic risk factors associated with the development of angle closure.

Risk factors other than shallow ACD and narrow anterior chamber angle have also been reported. For example, in the community-based study conducted in Japanese residents aged ≥40 years old, rapid shallowing of the ACD assessed by scanning peripheral anterior chamber depth analyser (SPAC) grades were demonstrated to be associated with angle closure development (Kashiwagi et al. 2013). The ACD grades provided by SPAC were obtained by quantitatively measuring ACD in a non-contact fashion from the optical axis to the limbus and comparing with the ACD values derived from a sample of Japanese subjects (Kashiwagi et al. 2004). In our study, the central ACD was measured using A-scan, but with different machines and different positions of subjects when measuring at baseline and at follow-up. Hence, we could not investigate the association of shallowing of central ACD with the development of angle closure.

Increased LT has also been reported as risk factors associated with angle closure development in Indian and Chinese populations (Vijaya et al. 2013; Wang et al. 2019). Moreover, hyperopia, shorter AL and anteriorly positioned lens were found to be associated with angle closure development in Indian population (Vijaya et al. 2013). We did find the differences in LT, AL, ALP and RLP between the subjects who developed angle closure and those did not but failed to demonstrate the association between these variables and the development of angle closure. It should be noted that in these two studies, there were relatively higher ratios of developed PAC/PACG and relatively lower ratios of developed PACS during the follow-up of 6 years and 10 years, respectively, compared with those in our study during the 5-year follow-up. Hence, this might be the reason.

The strength of our study lies in the population-based cohort design with international standardized protocols and data collected by trained researchers under strict quality control.

Table 4. Summaries of previous studies of the development of angle closure and related risk factors

Authors	Location	Setting	Subjects, number	Duration	Development of Angle Closure	Risk factors	Study type	Year of publication
Alsbirk PH	Greenland	Population	Eskimos with an age of ≥30 years old who had a limbal ACD graded as 0 or 1 using the van Herick test, or a value of 2 plus central ACD ≤2.70 mm, 75	10 years	8% (95% CI, 4%–12%) of normal (open angles on gonioscopy) developed PAC or PACG	Limbal ACD and central ACD	Prospective cohort study	1992
Wilensky JT, et al	America	Hospitals	Predominantly Caucasian participants with central ACD <2 mm or narrow anterior chamber angle, 129	Over 5 years (mean of 2.7 years)	19.3% developed angle closure (32% AAC and 68% chronic angle closure)	Not reported	Prospective cohort study	1993
Erie JC, et al.	America	Population	Residents of Olmsted County, Minnesota aged ≥40 years old, 28 731 in 1980 to 38 774 in 1992	13 years	8.3 per 100 000 people (95% CI, 5.6 to 11.0) developed PACG (44% acute PACG, 42% chronic PACG, and 14% intermittent PACG)	Not reported	Retrospective cohort study	1997
Ye TC et al.	China	Population	Chinese with a central ACD ≤2.0 mm or limbal ACD ≤1/4 of the corneal thickness or iris light band ratio ≤1/4 with oblique flashlight test, 485	5 years	4.1% developed angle closure (30% AAC, 40% chronic PACG and 30% PAC)	Shallow central ACD	Prospective cohort study	1998
Yip JL, et al	Mongolia	Population	Permanent residents of Suhkbaatar, Bayanzurkh and Chingltei districts of Ulaanbaatar or the province of Bayanhongor aged ≥50 years old with a central ACD <2.53 mm, 201	6 years	20.4% (95% CI, 14.8% to 25.7%) developed PACS	Narrower angles as determined by modified van Herick grading and gonioscopy at baseline	Prospective cohort study	2008
Kashiwagi K, et al	Japan	Community	Japanese residents aged ≥40 years old, 331	5 years	5.5% (95% CI, 4.0%–7.6%) developed angle closure (58.8% PACS, 17.6% PAC and 23.5% PACG)	Shallow ACD and rapid shallowing of the ACD	Prospective cohort study	2013
Vijaya L et al.	India	Population	Participants from the Chennai	6 years	4.0% (95% CI, 3.3%–4.7%)	Higher IOP, increased LT,	Prospective cohort study	2013

Table 4 (Continued)

Authors	Location	Setting	Subjects, number	Duration	Development of Angle Closure	Risk factors	Study type	Year of publication
			Glaucoma Study (rural and urban south Indians aged ≥40 years old), 3350		developed PACD (65.7% PACS, 27.6% PAC and 6.7% PACG)	shorter AL, shallow ACD, anteriorly positioned lens, and hyperopia		
Wang LH, et al	China	Population	Participants from the Liwan Eye Study (urban Chinese age ≥50 years old), 620	10 years	20.5% (95% CI, 17.4%–24.9%) developed angle closure (82.7% PACS, 11.8% PAC and 5.5% PACG)	Greater baseline LT, shallower ACD and narrower angle width	Prospective cohort study	2019

AAC = acute angle closure, ACD = anterior chamber depth, AL = axial length, CI = confidence interval, IOP = intraocular pressure, LT = lens thickness, PAC = primary angle closure, PACG = primary angle closure glaucoma, PACS = primary angle closure suspect.

There are some limitations of this study. One of the main limitations in our longitudinal study is loss to gonioscopic examination at follow-up. At baseline and the 5-year follow-up, we did not perform gonioscopy on all subjects but only did so on those with LACD ≤40% of corneal thickness or other sign of glaucoma and suspects, as well as one in ten of the examined subjects each day. Liang et al had reported that at baseline, this strategy might miss some PACS and PAC (one in over 400 PAC cases) cases but were not likely to miss any PACG case (Liang et al. 2011). However, this same strategy for gonioscopic examination used at follow-up would cause bias in our study.

To address this issue, we compared available baseline parameters between the two groups who did and did not receive the follow-up gonioscopic examination. Our data suggested that subjects who received follow-up gonioscopic examinations tended to be older and female, have lower income, lower prevalence of hypertension, larger SE, shallower central ACD, thicker lens and shorter AL. Given that female gender, larger SE, shallower central ACD, thicker lens and shorter AL were risk factors for angle closure, the development of angle closure is likely to have been overestimated. The underrepresentation of men and those with higher income was probably due to occupational reasons: men and those with higher income were more likely to be at work during the examinations.

Secondly, in our study, after a duration of 5 years, 94.7% subjects with baseline open angle developed PACS, 5.3% developed PAC and no one developed PACG. The reason for no PACG developed in the follow-up might be the relatively short duration. Hence, caution is warranted in extrapolating the findings to all the spectrum of PACD.

Thirdly, gonioscopy is a subjective measurement using a standardized grading system, and therefore, inter-observer and physiological variation can alter the interpretation of the results. Last but not least, the study population was Chinese, and the results may not be extrapolatable to other racial / ethnic groups.

Conclusions

In conclusion, this study reported the development from baseline open angle to angle closure after a 5-year follow-up. The study confirmed that the mean angle width and central ACD were independent predictive risk factors for the development of any form of angle closure.

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Correspondence:
Ningli Wang, MD, PhD
Beijing Institute of Ophthalmology
Beijing Tongren Eye Center
Beijing Tongren Hospital
Capital Medical University
Beijing Key Laboratory of Ophthalmology and Visual Sciences
No. 1 Dong Jiao Min Xiang Street
Dongcheng District
Beijing
People's Republic of China
100730
Tel: +86-1058269920
Fax: +86-1058269920
Email: wningli@vip.163.com

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