Ten-Year incidence of primary angle-closure in elderly Chinese: The Liwan Eye Study

Synopsis In this 10 year follow-up study, the cumulative incidence of any forms of primary angle closure in phakic eyes was 20.5%(127/620), including 16.9%, 2.4% and 1.1% with incident PACS, PAC and PACG.

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Abstract

Purpose: To determine the 10-year incidence of all forms of primary angle closure in phakic eyes and its risk factors in an urban Chinese population aged 50 years and older.

Methods: Survivors of 1405 baseline participants were invited to attend the 10-year follow-up visit in the Liwan Eye Study. Participants with established baseline angle closure, including primary angle closure suspects (PACS), primary angle-closure (PAC), primary angle closure glaucoma (PACG), or those who underwent bilateral cataract surgery during the 10-year period as well as those who did not tolerate gonioscopic examinations were excluded from this analysis. Incident PAC was present when those with open angles at baseline developed angle closure in any form in either eye during the 10-year period.

Results: Among 791 participants who returned during the 10-year follow-up visit, 620 (78.4%) provided data on PAC incidence. The 10-year cumulative incidence of any forms of PAC was 20.5% (127/620, 95%CI: 17.4~24.9%) including 16.9%, 2.4% and 1.1% with incident PACS, PAC and PACG in either eye, respectively. In multiple logistic regression, significant risk factors for incident angle closure were greater baseline lens thickness (OR=1.82 per mm, P=0.003), shallower anterior chamber depth (OR=3.18 per mm decreased, P=0.010), narrower angle width (OR=1.63 per decreased angle width, P<0.0001).

Conclusions: Approximately 1 in 5 people aged 50 years and older developed some form of angle closure over a 10-year period. Small ocular dimensions and hyperopia at baseline were associated with the development of angle

closure.

Key words: incidence, primary angle closure suspect, primary angle closure，primary angle closure glaucoma

Introduction

Primary angle closure (PAC) is an important eye health problem, affecting an estimated 79.6 million people in 2020, of which 5.3 million will be blind. [1] The prevalence of PAC varies by race, with especially high rates among Chinese populations. It is estimated that China will be home to 48% of all PAC cases globally in 2020.[1] The PAC spectrum is divided into primary angle closure suspects (PACS), primary angle closure (PAC) and PACG. [2 3]

Data on the incidence of PAC is scarce. A study of an Indian population aged 40 years and older found that the incidence of PAC was 4.0% after 6-year follow-up periods (0.7% annually).[4] Among Inuit individuals with a shallow anterior chamber, 16% developed PACG at a 10-year follow-up visit. [5]A study of a Mongolian population aged 50 years and older found a PACS incidence of 20.4% among participants with a central anterior chamber depth (ACD) of <2.53 mm over a 6-year follow-up period.[6] To date, there have been no population based cohort studies of incidence of PAC among Chinese people.

We have previously reported the prevalence of PACS, PAC, and PACG in urban southern China.[7] The aim of the current study is to determine the 10-year incidence of any forms of PAC in phakic eyes in this Chinese population and its associated predictors.

Methods

Study population

The Liwan Eye Study was a population-based study initiated in 2003. A 10-year follow-up examination was conducted in 2013, following the same protocol. At baseline, 75.4% (1405 of 1864) of eligible subjects aged 50 years and older completed a comprehensive eye examination and a questionnaire interview regarding education, income, hypertension and diabetes mellitus (DM). All participants in the baseline study were invited to take part in follow up examinations 10 years later. This follow-up study included 791 participants (73.8% of survivors, 86.2% of eligible subjects) who returned for the repeat examinations in 2013.

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

Participants who were diagnosed with any form of PAC or primary open angle glaucoma (POAG) at baseline, and those who had bilateral cataract surgery during the 10-year follow-up (if it was unilateral cataract surgery, untreated eyes were used for outcome analysis) as well as individuals who did not tolerate gonioscopic examinations were excluded from analysis.

Study Procedures

Detailed information of the gonioscopic examination in the Liwan Eye Study has been described previously.[7] Briefly, all participants underwent slit lamp examination (SL-8Z; Topcon, Tokyo, Japan; with a D1x digital image system; Nikon, Tokyo, Japan), static and dynamic gonioscopy with a Goldmann-type, one-mirror lens (Haag Streit, Bern, Switzerland) at ×25 magnification by the same experienced ophthalmologist (MH), whose observations were standardized against those of an experienced gonioscopist (PJF).[7] A narrow beam of light 1 mm in length was used for static examinations. Care was taken to avoid the miotic effect of light on the pupil as well as inadvertent indentation. Dynamic examination with increased illumination was performed after static gonioscopy. The Shaffer system[8] was used to assess the degree of angle width in the superior and inferior quadrants and then was recorded using five categories (0°, 10°, 20°, 30°, and >40°). Iris insertion was recorded in five categories from A (anterior to Schwalbe's line) to E (with a very wide ciliary body band).

The definitions developed by ISGEO (International Society of Geographical and Epidemiological Ophthalmology) were used for various states of angle closure and are as follows[2]: PACS: an eye with 270 degrees or more in which the posterior pigmented trabecular meshwork could not be seen during a static examination with intraocular pressure (IOP) < 21 mmHg and no peripheral anterior synechiae (PAS), previous acute angle closure or glaucomatous optic neuropathy; PAC/G: an eye with 270 degrees or more in which the posterior pigmented trabecular meshwork could not be seen with established PAS and/ or IOP $\geq$ 21 mmHg and/ or glaucomatous optic neuropathy. Incident angle-closure was defined as occurring in participants with baseline open angles who developed any form of PAC (PACS or PAC/G) in either phakic eye during the 10 year follow-up period.

Noncycloplegic refraction were obtained using a handheld auto-refractor (ARK-30;Nidek, Crop, Gamagori, Japan) and spherical equivalent (SE) was calculated as sphere plus 1/2 of the cylinder. A-scan ultrasound (Echoscan US1800, Nidek Corp) was used to measure axial length (AL), ACD, lens thickness (LT), and central cornea thickness (CCT) before mydriasis. Absolute lens position (ALP) was defined as ACD＋1/2×LT and relative lens position (RLP) as ALP/AL. IOP was measured before mydriasis using a handheld tonometer (Tonopen; Mentor, Norwell, Massachusetts, USA). All participants underwent height and weight measurement. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters.

Statistical analysis

All statistical analysis was performed using Stata (ver. 10.0; StataCorp., College Station,TX). The 10-year incidence of any form of angle-closure by age and gender were calculated. Student's t-tests was used to compare continuous variables, while Pearson X2 or Fisher's exact test was used for the comparison of categorical data. We used ocular factors of the right eye for cases where either both eyes and the right eye only developed PAC. For those with incident PAC only in the left eye, ocular factors of the left eye were used. Multivariate logistic regression models were used to identify the baseline risk factors for the occurrence of any angle-closure. 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 incident any forms of PAC. Statistical significance was defined as a p-value of < 0.05.

Results

Of the 1405 participants in the baseline examination, 320 (22.8%) were deceased, and 167 (11.9%) had relocated outside of the study area during 10-year follow-up. Another 127 (9.0%) refused to attend to the final visit, leaving 791 (72.9% of the survivors) with a mean baseline age of 62.3±8.7 years who completed the 10-year follow-up (Figure 1). The 791 attendees tended to be younger, male, and were more likely to have hypertension (**Supplemental Table 1**).

Among the 791 participants who completed the 10-year follow-up examination, a total of 620 (79.4%) with a mean age of 60.9 ± 8.3 years had sufficient data to determine the incidence of PAC (**Figure1**). The 171 (21.6%) excluded participants included those with any forms of PAC (69, 40.4%) or POAG (9, 5.3%) at baseline, those who had undergone bilateral cataract surgery during the follow-up period (47, 27.5%), and those with missing data on gonioscopy (46, 26.9%).

The overall 10-year incidence of any form of PAC was 20.5% (127/620, 95%CI: 17.4~24.9%). PAC incidence did not increase with age overall, but women 70-79 years of age had a higher incidence (28.6% [95%CI: 17.3~42.2%]) than those 50-59 years (21.3% [95% CI: 15.6~28.0%]). (**Table 1**)

PACS was the most common form of angle closure to develop, with 105 of 127 incident cases (82.7%) being classified as PACS. The 10-year incidence of PACS was 16.9 % (95%CI: 14.1~20.1%) and incident PACS increased with age among females, from 19.1% (95% CI: 13.7%~25.6%) in the 50-59 year to 23.2% (95%CI: 13.0%~36.4%) in the 70-79 years although this was not statistically significant. Women overall were more likely to develop incident angle closure than men (19.8% vs 13.4%, P=0.03). 22 of the 127 incident cases who developed incident PAC/G included 15 cases of PAC and 7 cases of PACG in either eye. Therefore, the incidence of PAC was 2.4% (95% CI:1.4%~4.0%), and the incidence of PACG was 1.1% (95% CI: 0.5%~2.3%). Among the 15 eyes with PAC, 3 were presented with an elevated IOP, 11 were had PAS, and 1 had both an elevated IOP and PAS. (**Table 1**)

Compared to those who did not develop any form of angle closure over the 10-year period, incident cases were more likely to be female (P=0.01), had narrower angle width (2.56±1.01 vs 3.33±0.90, P<0.001), had thicker lenses (4.48±0.63 mm vs. 4.13±0.63 mm, P<0.001), had shorter AL (22.7±0.82 mm vs. 23.5±1.37 mm, P<0.001), had shallower ACD (2.57±0.28 mm vs. 2.80±0.33 mm, P<0.001), and had a more hyperopic SE (0.58D vs. -0.59D, P<0.001) at baseline (**Table2**). **Figure 2** presents the relationship between 10-year incidences of angle closure and AL, ACD and LT. The incidence increased dramatically in eyes shorter than 22 mm in axial length and in those with ACD less than 2.5 mm and LT of more than 5.0 mm.

In multivariate logistic regression, significant risk factors for incidence of any form of PAC were: thicker LT (OR=1.82 per millimeter, 95%CI: 1.24~2.69, P=0.003), shallower ACD (OR=3.18 per millimeter decrease, 95%CI: 1.32~7.70, P=0.010), narrower angle width (OR=1.63 per decreased angle width grade, 95%CI: 1.26~2.11, P<0.001), shorter AL was marginally associated with incidence of any form of PAC. (OR=1.29 per diopter, 95%CI: 0.98~1.70, P=0.071, **Table 2**).

We used ROC analysis to assess the potential performance of ACD, LT, and AL as determinants of incident PACS, PAC/G and any Angle closure. The AUC was 0.728(95%CI:0.674~0.783), 0.686(95%CI:0.621~0.749), and 0.687 (95%CI:0.632,0.742), with best cut-off values of 2.60, 4.72, and 22.92 mm for ACD, LT, and AL, respectively for predicting incident PAC spectrum. The sensitivity and specificity was 74.1% and 57.1% for ACD with best cut-off values, while the corresponding figures were 46.3% and 82.6% for LT, and 65.4% and 60.9% for AL. (**Table3 and Supplemental Figure1**).

Discussion

The cumulative incidence of any form of PAC over the 10-year period in this population-based sample of Chinese individuals was high, 20.5%, but most of the angle-closure were mild and did not result in elevated IOP or PAS. This is the first population-based study evaluating the incidence of PAC among elderly Chinese individuals, a high-risk population for angle closure. As in previous cross-sectional studies,[9] [10]greater LT, shallower ACD, narrower angle width, and more hyperopic SE at baseline were predictors for the development of angle closure.

Available data on incidence of various forms of PAC are summarized in **Supplemental Table 2.** We found a substantially higher incidence of angle closure (2.05% annually) than was reported in an Indian population aged 40 years and older (0.7% annually).[4] In a study of a high-risk Mongolian population aged 50 years or older with ACD < 2.53mm, the 6-year incidence of PACS was 20.4%.[6] If we look only at this group of individuals, with similar cutoff in the present study, the incidence was 25.6% (2.56% annually), which was lower than what was found in the Mongolian population. A 10 year follow-up study of Greenland Inuit persons with ACD≤2.70 mm or limbal ACD < 1/4CT at baseline showed 16% developed angle closure,[5]less than what was found in our study. The consistently high incidence in Inuit, Mongolian and Chinese population[11 12] supported the theory that people with East Asian background have higher risk of angle closure.

We further observed that the incidence was higher in females. A higher incidence of PAC among women has been consistently found in previous research, including the Mongolian[6] and Inuit[5]studies noted above. Such a difference was not seen in the study from India, but most population-based studies have found that women have nearly three-fold higher prevalence of angle closure. [4]

Cross-sectional studies consistently suggest that older people have a higher prevalence of angle closure but this could be attributable to either a genuine aging effect or cohort effects. A cohort effect is suggested if a group of people’s life experience influences the outcome of interest, for example, a more recently born cohort of people may have been exposed to better education, leading to higher rates of myopia which might results in deeper ACD and lower rates of angle closure. The incidence data observed in the current study found a higher incidence of angle closure in older people and therefore appears to suggest the increased prevalence of PAC in older people may largely be attributable to aging effects. This conclusion seems to be further supported by another of our studies where we observed significant reduction on ACD in 2-year follow-up of older Chinese. [13]Interestingly, the Chennai Eye Study reported that the incidence of any form of PAC decreases with age, but this may partly be explained by a much higher number of cataract surgeries being performed in the Indian population. One study using data from Myanmar [14] estimated that if cataract surgery were performed on 8.8% of eyes with visually significant cataract, it would reduce the incidence of angle closure in the adult population by 38.5%. Therefore it is likely that our study underestimates the true incidence of angle closure since our study subjects were engaged with the eye care system and many received cataract surgery.

The important risk factors for incident angle closure, shallower ACD, thicker LT, and narrower angle width have consistently been shown to be associated with angle closure in previous cross-sectional and longitudinal studies.[4 9 15 16]Therefore, these biometric factors are often used as indicators for screening to identify the people at risk on developing PAC and PACG although most of these analysis are based on cross-sectional data. Our study is perhaps the first longitudinal study assessing the efficacy of these parameters in “predicting” the onset of any forms of PAC in the future. Most of the cross-sectional studies reported a much better performance using ACD as a screening tool, with AUC of 0.85 or greater, [17-20] which is much higher than what we observed in this longitudinal study. None of these parameters have strong enough predictive ability to warrant their use in determining who requires more intensive monitoring.

The strength of this study lies in the population-based cohort design with standardized protocols and data collected by trained researchers. In addition, gonioscopy examinations were performed by a single, experienced ophthalmologist to ensure the consistency of results. The main limitation of this study is loss to follow-up, although our data suggest that the participants and non-participants did not differ in terms of ocular parameters. Another limitation of this study is the lack of successful completion of gonioscopy among participants in the older age groups who were unable to cooperate with gonioscopy. As the rate of angle closure is expected to be higher in older people, this may perhaps result in an underestimation in the overall incidence. In addition, the number of observation in very old cohort (80 years and older) is small with insufficient power to estimate the incidence. However, all these problems should not have affected the age-specific rates unless those who could not undergo gonioscopy were likely to have angle closure. One should also note that during 10 years follow-up, 47 people who had received cataract surgery were removed from the analysis, possibly biasing the estimation on incidence rate.

In conclusion, this study is the first to report the 10-year incidence of any forms of PAC in a population-based sample of Chinese elderly. The study confirmed the incidence of PAC increasing with age, also confirmed that the biometric anatomic parameters including shallower ACD, thicker LT, narrower angle width, and more hyperopic SE are independent predictive factors for the development of angle closure. While the incidence of any form of PAC was high, over 20%, the overwhelming majority was angle crowding with no clear adverse effect on the health of the eye. Teasing apart who will and will not develop angle closure and high eye pressure or glaucoma will require even larger cohorts to be followed.

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Table legends

Table1 Ten-year incidence of any forms of primary angle-closure disease by age and gender in the Liwan Eye Study

Table2 Baseline Characteristics of Participants who did and did not develop incident of any forms of Primary Angle-Closure in the Liwan Eye Study

Table3 Baseline predictors for 10-year Incident any forms of Primary Angle-Closure in the Liwan Eye Study.

Table5 Area Under the Curve, Best Cutoff, and Odds Ratios (ORs) of Ocular Parameters at Baseline for 10-years Incident Primary Angle-Closure.

Figure legends

Figure 1 Flow chart showing the enrollment of participants in the Liwan Eye Study.

Figure 2 10-year incidence of any forms of primary angle closure and association with axial length, anterior chamber depth and lens thickness in right eyes in Liwan Eye Study. A: association with anterior chamber depth; B: association with lens thickness; C: association with axial length.

Supplemental table legends

Supplemental Table1 Baseline characteristics of participants who did and did not return for the 10-year follow-up examination.

Supplemental Table2 Comparisons of efforts to determine the incidence of primary angle closure.

Supplemental figure legends

Supplemental Figure 1 The receiver operating characteristics (ROC) curve of ACD on discriminating people who had versus who didn’t have incident PAC in the Liwan Eye Study.

Table 1 Ten-year incidence of any forms of primary angle-closure disease by age and gender in the Liwan Eye Study

Age at baseline (years)	All		Male		Female	
	n/N	% (95%CI)	n/N	% (95%CI)	n/N	% (95%CI)
PACS in either eye						
Age (yrs)						
50-59	52/319	16.3 (12.4,20.8)	17/136	12.5 (7.5,19.3)	35/183	19.1 (13.7,25.6)
60-69	36/186	19.4 (13.9,25.8)	16/88	18.2 (10.8.27.8)	20/98	20.4 (12.9,29.8)
70-79	17/106	16.0 (9.6,24.4)	4/50	8.0 (2.2,19.2)	13/56	23.2 (13.0,36.4)
80+	0/9	0	0/3	0	0/6	0
Total	105/620	16.9 (14.1,20.1)	37/277	13.4 (9.6,17.9)	68/343	19.8 (15.7,24.4)
PAC/G in either eye						
Age (yrs)						
50-59	7/319	2.2 (0.9,4.5)	3/136	2.2 (0.5,6.3)	4/183	2.2 (0.6,5.5)
60-69	9/186	4.8 (2.2,9.0)	2/88	2.3 (0.3,8.0)	7/98	7.1 (2.9,14.2)
70-79	5/106	4.7 (1.5,10.7)	2/50	4.0 (0.5,13.7)	3/56	5.4 (1.1,14.9)
80+	1/9	11.1 (0.3,48.2)	0/3	0	1/6	16.7 (0.4,64.1)
Total	22/620	3.6 (2.2,5.3)	7/277	2.5 (1.0,5.1)	15/343	4.4 (2.5,7.1)
Any PAC disease in either						
Age (yrs)						
50-59	59/319	18.5 (14.4,23.2)	20/136	14.7 (9.2,21.8)	39/183	21.3 (15.6,28.0)
60-69	45/186	24.2 (18.2,31.0)	18/88	20.5 (12.6,30.4)	27/98	27.6 (19.0,37.5)
70-79	22/106	20.8 (13.5,29.7)	6/50	12.0 (4.5,24.3)	16/56	28.6 (17.3,42.2)
80+	1/9	11.1 (0.3,48.2)	0/3	0	1/6	16.7 (0.,64.1)
Total	127/620	20.5 (17.4,24.9)	44/277	15.9 (11.8,20.7)	83/343	24.2 (19.8,29.1)

Table 2 Factors associated with 10-year Incidence of any forms of Primary Angle-Closure in the Liwan Eye Study.

Baseline characteristics	Participants who developed incident Primary Angle-Closure disease N(%)	Participants who did not develop Incident Primary Angle-Closure disease N(%)	Univariate Logistic Regression		Multivariate Logistic Regression	
			OR (95% CI)	P value	OR (95% CI)	P value
Number of participants	127 (20.5)	493 (79.5)				
Age(years)	61.1±7.72	60.8±8.48	1.0 (0.98, 1.03)	0.753	0.97 (0.95,1.00)	0.079
Female	83 (65.4)	260 (52.7)	1.69 (1.13,2.54)	0.011	1.15 (0.71,1.84)	0.580
Education, none	24 (19.1)	70 (14.7)	1.37 (0.82,2.29)	0.227		
Low income, <1000 RMB/Month	72 (75.8)	244 (69.1)	1.40 (0.83,2.35)	0.207		
Diabetes, present	8 (6.4)	40 (8.3)	0.75 (0.34,1.64)	0.464		
Hypertension, present	52 (41.6)	195 (40.5)	1.04 (0.70,1.56)	0.830		
BMI(kg/m^2)	23.4±3.30	23.6±3.03	0.98 (0.91,1.05)	0.510		
Mean Angle Width	2.56±1.01	3.33±0.90	2.15 (1.75,2.63)	<0.0001	1.63 (1.26,2.11)	<0.0001
AL(mm)	22.7±0.82	23.5±1.37	2.09 (1.63,2.69)	<0.0001	1.29 (0.98,1.70)	0.071
ACD (mm)	2.57±0.28	2.80±0.33	13.0 (6.13,27.6)	<0.0001	3.18 (1.32,7.70)	0.010
LT (mm)	4.48±0.63	4.13±0.63	2.93 (2.05, 4.19)	<0.0001	1.82 (1.24,2.69)	0.003
Absolute Lens Position	4.80±0.35	4.86±0.44	0.84 (0.52,1.36)	0.478		
Relative Lens Position	2.11±0.15	2.07±0.18	6.32 (1.94,20.7)	0.002		
SE(D)	0.58±1.28	-0.59±2.82	1.31 (1.14,1. 49)	<0.0001		
IOP(mmHg)	15.1±3.06	15.4±3.06	0.96 (0.90,1.02)	0.216		
CCT(μm)	544±31.5	541±33.5	1.00 (0.99,1.01)	0.434		

Abbreviations: BMI=body mass index, AL=axial length, ACD=anterior chamber depth, LT=lens thickness, SE=spherical equivalence, IOP=intraocular pressure, CCT=central cornea thickness, OR=odds ratio, CI=confidence interval

Table 3 Area Under the Curve, Best Cutoff, and Odds Ratios (ORs) of Ocular Parameters at Baseline for 10-years Incident Primary Angle-Closure.

Ocular biometry at baseline	Best Cutoff	Area Under Curve(95%CI)	Sensitivity(%)	Specificity(%)
PACS				
ACD (mm)	2.59	0.725 (0.665,0.785)	74.3	58.3
LT (mm)	4.72	0.672 (0.596,0.747)	44.7	80.6
AL (mm)	22.92	0.663 (0.601,0.726)	64.0	59.7
PAC/G				
ACD (mm)	2.70	0.674 (0.561,0.786)	57.7	70.0
LT (mm)	4.37	0.678 (0.582,0.775)	53.7	90.0
AL (mm)	22.87	0.711 (0.609,0.813)	65.2	65.0
Any PAC disease				
ACD (mm)	2.60	0.728 (0.674,0.783)	74.1	57.1
LT (mm)	4.72	0.686 (0.621,0.749)	46.3	82.6
AL (mm)	22.92	0.687(0.632,0.742)	65.4	60.9

Abbreviations: PACS=primary angle closure suspect, PAC/G=primary angle closure/glaucoma, ACD=anterior chamber depth, LT=lens thickness, AL=axial length