# CLINICAL SCIENCE

# Five year risk of progression of primary angle closure suspects to primary angle closure: a population based study

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**Aim:** To report progression of primary angle closure suspects (PACS) to primary angle closure (PAC) at the 5 year follow up of a population based sample.
**Methods:** 82 of 118 PACS who could be contacted and 110 randomly selected normals from a population based survey in 1995 were invited for a follow up examination in 2000. Progression to PAC was based on the development of raised IOP or synechiae in a PACS.
**Results:** 50 of the 82 PACS contacted were examined. 11 (22%; 95% CI 9.8 to 34.2) developed PAC (seven synechial and four appositional); all were bilateral PACS. Two of 50 people previously diagnosed as PACS were reclassified as normal. One person among the 110 normals progressed to PAC. The relative risk of progression among PACS was 24 (95% CI 3.2 to 182.4). There was no significant difference in axial length, anterior chamber depth, or lens thickness between those who progressed and those who did not. None of the patients developed optic disc or field damage attributable to angle closure. One angle closure suspect was diagnosed to have normotensive glaucoma.
**Conclusion:** In this population based study of PACS the 5 year incidence of PAC was 22%; none developed functional damage. Bilateral PACS was a clinical risk factor for progression.

While glaucoma is recognised as a major cause of ocular morbidity worldwide, the pattern of disease prevalence varies in different parts of the world. Quigley estimated that 66.8 million people are affected by glaucoma worldwide and 6.7 million are bilaterally blind because of the disease. Extrapolating data from the rest of Asia to India he estimated that there would be eight million people affected with glaucoma by the year 2000 with a 1:1 prevalence of open angle to angle closure glaucoma.[1]

It has been a clinical impression in India that primary chronic angle closure glaucoma (PACG) is more common than primary open angle glaucoma (POAG).[2] The Andhra Pradesh eye disease survey (APEDS) from India suggested that chronic PACG is commoner than thought; 0.7% of the population over the age of 30 years had PACG; 1.4% over the age of 30 years (2.2% >40 years) had occludable angles at risk for angle closure.[3] A smaller population based study the Vellore eye study (VES) also from south India found that PACG (4.3%) was commoner than POAG (0.4%).[4] Definitions and methodology can explain some of the differences between the studies.[5] Using the same definition the prevalence of PACG in the latter report, 0.5%, is very similar to the former: 10.35% of the VES population was considered to have occludable angles; this is higher than the rate (6.4%) reported from Mongolia.[6] It is becoming increasingly obvious that angle closure may be a major problem in India.

A recently suggested survey terminology for patients with narrow or occludable angles predisposing to PACG is primary angle closure suspect (PACS). The presence of raised intraocular pressure (IOP) and or peripheral anterior synechiae in a PACS is termed primary angle closure (PAC) and the term primary angle closure glaucoma (PACG) is used only in the presence of disc and field damage with PAC.[7]

Laser peripheral iridotomy (LPI) is a relatively innocuous procedure with good success rates and could be used prophylactically for PACS; however, management should be based on the risk of progression of PACS to angle closure and glaucoma.

We need to know the number of occludable angles that will progress to ACG, the time frame over which this occurs, factors that predict progression, and the risk of blindness from such progression. Without such definitive data it may not be appropriate to advocate laser peripheral iridotomies for all occludable angles.[8] A recent report did suggest this approach, but we calculate that such a policy would mean treating one in six of the population.[5 9] In the developing world this will probably overburden an already stressed eye care delivery system. In our own institution, unless indicated by logistical difficulties, people with occludable angles are usually given an explanation of the symptoms of acute closure and advised on follow up.

There are scanty data on the natural history of PACS. A single clinic based study provided some indication of progression in PACS followed up for a mean duration of 2.7 years.[10] A high risk sample of Eskimos (shallow chamber at the limbus) reported that 8% of normal (angles open on gonioscopy) and 35% of PACS (on gonioscopy) progressed to PAC or PACG over 10 years.[11]

Five years after a population based survey, we evaluated angle closure suspects for progression to angle closure. For comparison, randomly selected normals from the same study were also re-examined at the same time.

## METHODS

This population based prospective study was conducted at Schell Eye Hospital, Christian Medical College, Vellore, a tertiary care referral centre.

Vellore is a town in south India, 140 km south west of Chennai. In 1991 it had a population of 304 713 (153 863 males and 150 850 females). In 1995 using a stratified simple random sampling technique we had identified a study population of 1932 people from 12 random clusters of a defined urban population. This population was invited to participate in the Vellore eye survey (VES). All patients lived

within 5 km of the department. Details of the survey methodology and results of the VES have been published earlier.[4] Of relevance here is the diagnosis of PACS, PAC, and PACG.

In 1995, gonioscopy was performed on all individuals using a Goldmann two mirror gonioprism (Haag-Streit) under standard testing conditions in dim ambient illumination with a shortened slit beam that did not impinge upon the pupil. The preferred grading used for gonioscopy in our institution is based on structures actually visualised; we have reported good agreement for this method.[12][13] A forced choice was made to classify an angle as PACS or normal. This was considered necessary for survey purposes. Examination for the presence of peripheral anterior synechiae (PAS) was performed by manipulating (applying slight pressure on the lens as the patient looked towards the mirror) with the Goldmann double mirror goniolens. For this purpose the observer first used the Goldmann goniolens as described; if the angle could not be opened, the Sussman four mirror lens was used to perform indentation gonioscopy.

Newer terminology recommended for glaucoma surveys has recently been published.[7] At the time of the initial examination in 1995 as well as the subsequent examination in 2000, this newer terminology was not in use and the definitions used were different. In the interests of uniformity we adopted the suggested terminology, as far as the recorded data permitted.

Accordingly, primary angle closure suspect was defined as non-visibility of the filtering trabecular meshwork for 180 degrees or more, intraocular pressure (IOP) below 22 mm Hg, and no peripheral anterior synechiae in the angle. A "normal" (not occludable) angle was one where the posterior third of the trabecular meshwork was visible for more than 180 degrees. As the data were recorded for 180 degrees during both examinations, it was not possible to report this for 270 degrees as suggested in the new terminology. Except for this extent of non-visibility of the trabecular meshwork, the definition was similar to PACS according to the newer terminology.[7]

Primary angle closure (PAC) was classified as synechial or appositional. Primary (appositional) angle closure was defined as raised IOP (>21 mm Hg) associated with non-visibility of the filtering trabecular meshwork for more than 180 degrees, in the absence of peripheral anterior synechiae, disc damage, or field changes. Primary (synechial) angle closure was defined as presence of peripheral anterior synechiae with non-visibility of the filtering trabecular meshwork for more than 180 degrees, with or without a raised IOP (>21 mm Hg), without disc damage or demonstrable field defects. The presence of even a single synechia was considered significant. Other causes of synechiae were excluded.

The term primary angle closure glaucoma (PACG) was only used if disc and field changes were present with PAC (appositional or synechial) as defined.

In September 2000, all people previously diagnosed to be PACS were invited for a review examination. Of the 972 people examined in 1995, 181 eyes of 118 patients (10.5 %) were considered to be PACS. Sixty three patients were bilateral PACS and 55 were unilateral suspects.

To obtain the relative risk of progression in PACS we also examined 110 normal subjects (with gonioscopically open angles) from the original population. The original sample had been selected randomly. The 110 normals were again selected in a random manner as follows: people who participated in the previous study were assigned hospital numbers in chronological order. From the database we extracted information regarding which population cluster they belonged to and arranged them in chronological order of the date of examination in the hospital. The first 25 previously diagnosed normal people from each cluster were identified and invited for examination. The next 10 people were short listed. If a person from the first list could not be contacted, the next (short listed) person was

contacted. A total of 300 people were identified and 110 short listed. The incentive offered was free examination and treatment at the hospital.

These individuals were approached by a social worker and invited to undergo follow up examination at the hospital. All selected individuals were given a specific date for examination. In case of non-response the social worker once again contacted the selected individual population and a fresh appointment date was fixed. If the second appointment was also missed, the next person on the short list from that cluster was invited for examination.

Examination for both groups was performed in a masked manner; the examiner was unaware of the previous examination results. All people first underwent visual acuity testing and refraction by one of two optometrists. Data on age, sex, past medical and eye history were obtained using an interviewer administered questionnaire. Specific inquiries were made regarding a history of glaucoma and history suggestive of angle closure glaucoma.

All participants underwent a complete ophthalmological examination performed by a single qualified ophthalmologist who had worked for at least 2 years in the glaucoma clinic under the guidance of a glaucoma specialist.

A complete ophthalmological examination included slit lamp examination with a Haag-Streit 900 slit lamp. Goldmann applanation tonometry was performed on all patients; the mean of three consecutive readings was used for analysis. Any patient with an IOP >21 mm Hg was advised to have daytime diurnal pressure measurements. Ocular biometry measurements (axial length, anterior chamber depth, and lens thickness) were obtained in all patients using the Tomey model AL 1000 by one of two observers. The probe was centred over the undilated pupil and a mean of three consecutive readings taken. For analysis, one eye of normals and bilateral PACS was randomly selected using computer generated random blocks. In people considered to be PAC suspects unilaterally, only that eye was used for analysis.

For the sake of uniformity, gonioscopy was performed on all individuals using a Goldmann two mirror gonioprism under standard testing conditions described for the first survey; the angle graded and a forced choice of normal or PACS was made.[4][12] The only difference from the previous examination was that following the two mirror examination, indentation gonioscopy using the Sussman gonioscopic lens was performed in all subjects.

After gonioscopy, patient data were unmasked and examination findings were compared with the previously recorded findings. The glaucoma specialist confirmed findings in patients with any change in gonioscopic diagnosis.

The optic disc was examined stereobiomicroscopically (using a 78D lens) after dilatation and recorded as in the first survey.[4] All cases with suspicious or glaucomatous optic discs, raised IOP (>21 mm Hg), or gonioscopic progression were advised to undergo visual field examination (SITA Standard).

The $t$ test was used to compare ocular biometry results between those who progressed and those who did not. The $\chi^2$ test was used to compare differences in proportions between groups.

## RESULTS
### PACS
From the earlier study 118 PACS were identified and invited for a follow up examination. Of the 118 patients 82 could be contacted (34 shifted residence to an unknown address and two had died). Among those contacted, two were too infirm, one refused examination, and 29 did not keep their appointments despite repeated requests.

Of the 50 PACS who responded, 38 were bilateral suspects and 12 unilateral. The response rate among bilateral PACS (38

**Table 1**  Age distribution of cases progressing to angle closure

| Age (years) | PACS (total) | PACS (examined) | PAC (% Age) |
|---|---|---|---|
| 36–45 | 14 | 14 | 2 (14.3%) |
| 46–55 | 48 | 11 | 3 (27.3%) |
| 56–65 | 56 | 25 | 6 (24.0%) |
| Total | 118 | 50 | 11 (22.0%) |

PACS = primary angle closure suspect.
PAC = primary angle closure.

of 63) was better than among unilateral PACS (12 of 55). The mean age of the PACS group was 54.8 (SD 8.7) years for the responders and 55.5 (SD 8.1) among the non-responders. The male to female ratio among responders was 15:35; this was 26:42 for non-responders. The PACS who responded were also similar to the non-responders as regards refractive error and intraocular pressure at the first visit. In the intervening 5 years, four of 12 unilateral PACS had progressed to bilateral PACS.

Eleven of the 50 PACS (22%; 95% CI 9.80 to 34.2) had progressed to PAC. Seven developed synechial PAC, and four developed appositional PAC. Those who progressed were bilateral PACS; the difference in progression between bilateral and unilateral PACS was statistically significant (p <0.05). The progression was bilateral in five of the PACS and unilateral in six. Three of 15 males and eight of 35 females progressed to PAC; this difference was not significant (p = 0.2). No one developed symptoms suggestive of acute angle closure glaucoma in the intervening period. There were no cases of blindness due to glaucoma. The age distribution of those who progressed is shown in Table 1.

One PACS had undergone bilateral laser iridotomy 3 years following the initial examination after developing synechial PAC. He also had proliferative diabetic retinopathy without signs of angle or iris neovascularisation. This person was considered to have progressed to PAC as defined. One PACS had undergone bilateral cataract surgery elsewhere in the past 5 years. The angles were wide open with IOP of 18 mm Hg in the right eye and 16 mm Hg in the left eye and normal discs. PAS were present only in some areas of the cataract wound.

One PACS developed bilateral glaucomatous disc changes and early visual field loss. IOP recordings including a day/night phasing were below 19 mm Hg. The angle grade remained the same, corneal thickness was normal, and there was no increase in IOP in the mid dilated position using tropicamide. The angle grading remained unchanged in the mid-dilated position. The person had systemic hypertension and a history of a 6 day hospitalisation for control of hypertension a year earlier. We did not feel that angle closure was responsible for the glaucoma.

Two people previously diagnosed to be PACS were considered to be gonioscopically open at the follow up visit; both were unilateral. One person previously considered to be normal developed bilateral synechial PAC. No other cases were considered to have been misclassified. The kappa statistic for agreement for PACS between the two phases of the study was 0.96.

Clinically, three PACS developed visually significant cataracts (accounting for best corrected vision less than 6/18). None of these eyes were considered to have progressed to PAC.

There was no statistically significant difference in ocular biometry measurements between those who progressed and those who did not (Table 2)

### Normals

In all, 300 normal people were contacted for 110 to respond (75 had changed residence and could not be traced, 23 could not be contacted, 10 had died, one was invalid and could not come to the hospital, one person refused examination, and 90 did not come for examination despite repeated requests). The mean age of normals (49 years (SD 8.5)) was younger, but not significantly different from PACS. The male female ratio was 45:65.

One normal was diagnosed to have bilateral synechial PAC. This person had an IOP of 22 mm Hg in the right eye and 24 mm Hg in the left eye and glaucomatous discs but reliable fields could not be obtained despite repeated testing. Four people were considered to have developed ocular hypertension; only two of them continued to have raised IOP during a daytime diurnal variation. Six of the normals developed visually significant cataracts (best corrected vision less than 6/18). None of these eyes were considered to have progressed to PACS or PAC.

The biometric parameters for normals are also shown in Table 2. The anterior chamber depth in normals is significantly deeper than the PACS group.

The rate of new PAC in those with PACS was compared to the rate of new PAC in the normal group to provide the relative risk. The relative risk for progression of PACS to PAC was 24.2 (95% CI: 3.2 to 182.4).

### DISCUSSION

Primary angle closure glaucoma is a potentially sight threatening disease. LPI is a relatively simple technique; its use in PACS is an attractive therapeutic measure. While LPIs are associated with little morbidity, some eyes may require multiple sessions, complications do occur, and relation to progression of cataract is a consideration.[14–17] A significant proportion of our population are PACS; a policy or prophylactic LPI would stretch the health system of any developing country.[8] LPI in PACS is best based on hard data indicating risks of progression to angle closure and more importantly the risk of disc and field damage with the attendant risk of blindness. This is especially so as LPI in early closure is very effective.[18]

To the best of our knowledge this report is only the second population based study on progression in PACS. Twenty two

**Table 2**  PACS: comparison of ocular biometry measurements between cases progressing to angle closure and cases not progressing

| | Non-progression (n=39) | Progression (n=11) | Statistical significance | Normal (n=110) | Statistical significance |
|---|---|---|---|---|---|
| | Mean (SD) | Mean (SD) | | Mean (SD) | |
| Axial length | 22.3 (0.8) | 22.1 (0.8) | 0.6 | 22.5 (0.8) | 0.7 |
| AC depth | 2.8 (0.5) | 2.7 (0.4) | 0.9 | 3.2 (0.4) | <0.01 |
| Lens thickness | 4.6 (0.7) | 4.2 (0.5) | 0.8 | 4.2 (0.5) | 0.7 |

per cent of PACS (95% CI 9.8 to 34.2%) progressed to PAC. A study in Eskimos reported 35% (95% CI: 14.1 to 55.9) progression in 20 PACS followed up over 10 years. Our progression rate (4.4% per year) is higher than the Eskimo data (3.5% per year), but the confidence intervals do overlap. None of the patients followed up in our study developed acute angle closure. The sample size is small and the true rate for acute angle closure could be as high as 6%.[19] We have been informed that two of the PACS among the Eskimos (10%; CI 0 to 23%) did develop an acute attack (Poul Alsbirk, personal communication).

While our criteria of 180 degrees non-visibility of the trabecular meshwork for the diagnosis of PAC suspects may appear lenient compared to the suggested terminology, it reflects our classification of angle closure at the time of the earlier survey. Reclassification according to non-visibility of the filtering meshwork (270 degrees) was hence not possible.[7] It is possible that such a definition would be more specific, but is perhaps too stringent (Paul Foster, personal communication). The Greenland study did not specify the degree of non-visibility of filtering meshwork required to label an angle as PACS.

We used a cut off of >21 mm Hg to define primary (appositional) angle closure, as this is what we had used in the first phase of the study. The mean IOP in the population we studied was 15.5 mm Hg.[4] If we use the cut off appropriate for our population (>22 mm Hg which is 2 SDs above the mean), two patients classified to have appositional closure would be excluded from the subset and the incidence of progression would become 18%.

One patient in normal group (0.9%) developed bilateral primary (synechial) angle closure. It is possible that he was misdiagnosed as normal at the initial visit especially since a forced choice was required to classify as PACS or normal. Alternatively, with age an angle can become occludable; 8% of non-occludable angles in Greenland Eskimos progressed.[11] The forced choice used in our study may also explain the large number of unilateral PACS. Four of 12 unilateral PACS did progress to bilateral PACS.

The other available data, clinic based, and with a more stringent definition also reports a similar incidence of progression of 19.4%.[10] The populations and follow up times were different and the mean age group was lower in our study. While it may intuitive to expect a higher rate in the clinic than in the population, this may not be the case if the condition is asymptomatic. Some of the cases followed up as PACS by Wilensky et al, would fit what we define as primary (appositional) angle closure. It is not clear whether occludable angles with small synechiae were included in that study. This is not specified, but their criteria for progression, synechiae more than one third of the angle, and the fact that 6.2% developed acute angle closure suggests that this might be the case. By our definition, many of their cases were not PACS but PAC (appositional and possibly synechial), conditions for which we would usually offer an LPI.

The progression rate was similar in both the 46–55 and 56–65 year age group (Table 1). This is a little surprising, as changes in lens thickness would be more with increasing age. This may be a matter of degree as those who developed visually significant cataract did not necessarily progress to PAC; among the normals they did not become PACS. Three of the PACS developed significant cataract but none progressed to PAC. The numbers are few and interpretation is further hindered by low response rate. Perhaps a longer follow up with more advanced lens changes would show a different picture.

The rate of new PAC in those with PACS was compared to the rate of new PAC in the normal group to provide the relative risk. The relative risk for progression of PACS to PAC is 24 (95% CI: 3.2 to 182.4). All progression occurred in bilateral PACS but could be due to differential examination rates. The relatively large number of unilateral PACS may be surprising but is probably explained by the protocol, which required a forced choice decision concerning PACS versus normal. And four of 12 unilateral PACS did progress to bilateral PACS. The important finding is that none of those who progressed developed disc and field changes (PACG). While this is again compatible with a true rate as high as 6%,[19] this finding, not reported in the two earlier studies, would seem to be critical from the management point of view. The relative and absolute risks of progression are high, but as none of our PACS developed PACG over 5 years, and none had acute angle closure, do we need really to worry about PACS in the short term? Are they a public health problem? Especially if cataract surgery is considered treatment for PACS and early PACG.[20 21] Certainly our patient who had cataract surgery had open angles and no evidence of glaucoma. In a country where an aggressive cataract surgical programme is likely to catch up with the patient, do we need to intervene with the laser at all? We should also bear in mind that LPI in early angle closure is very effective.[18] If it is feasible to wait for this early stage of anatomical damage before treatment, we would avoid many unnecessary iridotomies. We could not identify any biometric parameters that indicated eyes at risk for progression.

Our data suggest that unless there is some (as yet unknown) risk factor that can be identified, intervention for PACS is probably not required. There may be special situations like diabetics who require repeated dilatation, a "critical" looking angle, or logistical reasons for which the surgeon may feel more comfortable with an LPI; that will have to remain an individual decision.

In conclusion, this population based study on the natural history of PACS reports that as many as 22% may progress to PAC but none progressed to PACG. Accordingly LPI may not be warranted for PACS per se. However, our follow up was only for 5 years and the course of such angles over a longer period of time is unknown. Such information when available will better allow decisions for the long term.

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