# Clinical Presentation, Severity and Progression of Primary Angle Closure in Malays

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**SUMMARY**

**Introduction: There is limited knowledge on primary angle closure (PAC) in Malays. Understanding the clinical presentation and progression of PAC in Malays is important for prevention of blindness in Southeast Asia.**

**Material and methods: A retrospective record review study was conducted on Malay patients seen in the eye clinic of two tertiary hospitals in Kelantan, Malaysia. Based on the available data, Malay patients re-diagnosed as primary angle closure suspect (PACS), primary angle closure (PAC), and primary angle closure glaucoma (PACG) based on the International Society Geographical Epidemiological classification. Clinical data was collected from initial presentation including the presence of acute primary angle closure until at least 5 years follow up. Progression was defined based on gonioscopic changes, vertical cup to disc ratio (VCDR), intraocular pressure (IOP) and Humphrey visual field (HVF) analysis. Progression and severity of PACG was defined based Hodapp-Parrish-Anderson classification on reliable HVF central 24-2 or 30-2 analysis.**

**Results: A total of 100 patients (200 eyes) with at least 5 years follow up were included. 94 eyes (47%) presented with APAC. During initial presentation, 135 eyes (67.5%) were diagnosed with glaucomatous changes with 91 eyes already blind. After 5 years of follow up, 155 eyes (77.5%) progressed. There was 4 times risk of progression in eyes with PAC (p=0.071) and 16 times risk of progression in PACG (p=0.001). Absence of laser peripheral iridotomy was associated with 10 times the risk of progression.**

**Conclusion: Angle closure is common in Malays. Majority presented with optic neuropathy at the initial presentation and progressed further. Preventive measures including promoting public awareness among Malay population is important to prevent blindness.**

## INTRODUCTION

Angle-closure glaucoma (ACG) is a major cause of irreversible blindness in Asian populations [1]. The rates of primary angle closure glaucoma (PACG) are the second highest in East Asian populations after Mongolia and Myanmar[2-3]. The prevalence of PACG is believed to be lower in Southeast Asian populations when compared to China, but certainly higher than for Europeans.

Asia is home to more than 60% of the world's current population, with almost four billion people. Extensive studies on ACG have been conducted on the Chinese population when compared to other Asian populations. Malays are the third largest ethnic group in Asia and account for 5% of the world population [4]. There are approximately 300 to 400 million Malays living in Southeast Asia. The majority reside in Malaysia, Brunei, Indonesia, Thailand, and Singapore[5]. Therefore, it is important to study the clinical presentation of ACG among Malays as part of a strategy to prevent blindness. Identification of the factors that affect the clinical presentation and subsequent disease course of ACG is essential for better clinical management of this type of glaucoma that leads to blindness in Asia. Based on the Singapore Malay Eye Study (SiMES), the incidence of PACG, low vision and blindness was 0.12%, 18%, and 10%, respectively, in Malays residing in Singapore [5]. However, this data could be underestimated, as the total percentage of Malays in Singapore is rather small. Wong *et al*. found that Malay and Indian residents of Singapore contributed only half of the rates of admission for ACG when compared with Singaporean Chinese [6]. Based on our clinical observation, Malays seem to be severely affected at initial presentation with rapid progression. Furthermore, it was found that the progression rate was higher in Malays when compared to Chinese in a retrospective study that involved chronic angle closure glaucoma in Malaysia, Taiwan, and Hong Kong [7]. This finding was based on only 22 Malay patients.

Malaysia is a multiracial country comprised of 65% of Malays, 26% Chinese, 8% Indians, and 1% from other ethnic groups[9]. Malays are defined as a Malaysian citizen born to a Malaysian citizen who professes to be Muslim, habitually speak the Malay language, adhere to Malay customs, and are domiciled in Malaysia or Singapore [8]. Malaysia is comprised of 13 states. Kelantan is situated at the northeastern corner of Peninsular Malaysia where the majority of the population is Malay (93.3%)[9]. Thus, Kelantan is an ideal location to study on angle closure in Malays. Moreover, Malays are evenly distributed in urban, suburban, and rural areas. The objective of this study is to determine the clinical presentation, severity, and progression of angle

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closure among Malays in Malaysia. The clinical predictors for progression is also analysed in this study.

## MATERIALS AND METHODS

A retrospective record review was conducted involving patients with primary angle closure suspect (PACS), primary angle closure (PAC), and primary angle closure glaucoma (PACG) seen in two main tertiary hospitals in Kelantan, Malaysia: Hospital Universiti Sains Malaysia and Hospital Raja Perempuan Zainab II. The patients were seen between January 1998 and June 2010, with at least 5 years of follow up from their initial presentation. This study received ethical approval from the research and ethics committee of the School of Medical Sciences, Universiti Sains Malaysia.

Demographic data that included age at presentation and sex were documented. The details of signs and symptoms at first presentation include the presence of acute attack such as ocular or periocular pain, nausea, vomiting, blurring of vision with or without haloes around the light, and red eye were obtained from patient's medical record. Intraocular pressure (IOP) was measured with the Goldman applanation tonometer and the angle structure was visualized using two-mirror gonioscopic lens. Slitlamp biomicroscopic findings include the presence of glaukomflecken were also recorded. The first reliable documentation on vertical cup to disc ratio (VCDR) and Humphrey visual field analysis (HVF) based on 24-2 or 30-2 were also included. A reliable HVF was based on fixation losses less than 20% with false-positives and -negatives less than 33%. Diagnosis was made based on the recent definition of angle closure for prevalence survey [10]. Incomplete documentation such as missing angle evaluation was excluded. PACS is defined as an eye with appositional contact between the peripheral iris and posterior trabecular meshwork. PAC is defined as an eye with an occludable drainage angle and features to indicate that trabecular obstruction by the peripheral iris has occurred in the absence of glaucomatous optic disc damage. PACG is defined as PAC with evidence of glaucomatous optic nerve head damage with corresponding visual field defect.

Family history of glaucoma and systemic comorbidities such as diabetes mellitus, hypertension, ischemic heart disease, hyperlipidemia, migraines, and other conditions were obtained from patient's medical record. The initial and subsequent management includes medical treatment with systemic and topical pressure lowering drugs, laser peripheral iridotomy, or surgical peripheral iridectomy was documented. Lens extraction surgery, trabeculectomy, and other surgical intervention were also included.

Subsequent visual acuity, reliable HVF, and VCDR at the latest available follow up or at 5 years post initial presentation were included for further evaluation of progression. The progression from PACS to PAC was based on gonioscopic findings, VCDR, and IOP. The progression of PAC to PACG was based on HVF and VCDR. Two investigators; a glaucoma specialist and glaucoma subspeciality trainee (LS and AY) were responsible to assess the print out of HVF for severity and progression of PACG. The severity and progression of PACG was defined based on Hodapp-Parrish classification [11]. They were also responsible to determine the progression PAC and PACS. For the purpose of analysis, the recruited patients were divided into progression and non-progression groups. The date of progression and the duration of progression were documented to ascertain the rate of progression. Both eyes were included in this study, as each eye has a different clinical course.

Statistical analyses were performed using PAWS SPSS 18.0. Univariate analysis was done to compare the clinical presentation between non-progression and progression cases. Stepwise multiple logistic regression analysis was conducted to determine the predictive factors that affect the progression of angle closure. A p-value less than 0.05 was considered significant.

## RESULTS

A total of 100 Malay patients with PACS, PAC, and PACG were included. The clinical data of both eyes (200 eyes) was documented. Female to male ratio is near 4:1 (table I). Classical acute attacks were present in 94 eyes (47%). The majority presented with the chronic type of angle closure. Blurred vision was the most common symptom. History of glaucoma and blindness in the family were recorded in 3(3%) and 5 (5%) patients, respectively. Alarmingly, 30.4% presented with visual acuity of worse than 6/60 (table I). However, only 2 eyes were found to have mature cataracts and 15 eyes were found to have bullous keratopathy secondary to absolute glaucoma that impaired visualization of fundus. Thus, 17 eyes were excluded from evaluation of vertical cup to disc ratio and HFA. It is no surprise that 14 eyes presented with fully cupped discs and 41 eyes were already at an advanced stage of glaucoma at first presentation. A total of 58 patients were diagnosed with either bilateral or unilateral PACG on initial presentation.

After at least 5 years follow up, a total of 112 eyes (56.0%) progressed from PACS to PAC, PAC to PACG, and from mild to moderate PACG to advanced PACG. Although the majority progressed after 2 years of follow up, the highest percentage progressed within 6 months from the initial diagnosis. Based on student t-test, the progression of the disease was associated with higher IOP and more advanced HFA at initial presentation (table 2). The presence of APAC, poorer visual acuity, and advanced VCDR at the initial presentation was significantly associated with progression of the disease (table II).

A simple logistic regression module has identified baseline (or initial) IOP, MD, visual acuity, and peripheral iridotomy or iridectomy as significant clinical predictors associated with progression of the disease. However, apart from the above significant clinical predictors, age at the presentation and initial diagnosis were also added as potential predictors in our stepwise multiple logistic regression model. We found that for each year increase in age increases the risk of disease progression (OR 1.02; 95% CI 0.98, 1.06) (table 3). Similarly, every increase of MD (less negative value) of HVF was associated with protection against progression (OR 0.89; 95%

**Table I: Demographic and clinical presentation at initial presentation**

| Demographic data | N=100 |
|---|---|
| Age (year) | |
| Mean (SD) | 61.4 (8.4) |
| Range | 42-79 |
| Sex (n (%)) | |
| Female | 78 (78) |
| Male | 22 (22) |
| Clinical presentation (n (%)) | N=200 eyes |
| APAC | 94 (47.0) |
| Best corrected visual acuity | |
| 6/6-6/7.5 | 29 (14.6) |
| 6/9-6/12 | 57 (28.8) |
| 6/15-6/24 | 26 (13.1) |
| 6/30-6/48 | 18 ( 9.1) |
| ≥6/60 | 54 (27.3) |
| NPL | 14 ( 7.1) |
| Glaukomflecken | 11 ( 5.5) |
| Presence of peripheral anterior synechiae | 19 ( 9.5) |
| IOP (mmHg) | |
| Mean (SD) | 34.7(18.5) |
| Range | 18-70 |
| VCDR | |
| No fundus view | 17 ( 8.5) |
| 0.3-0.5 | 91 (45.5) |
| 0.6-0.7 | 37 (18.5) |
| 0.8-0.9 | 41 (20.5) |
| Fully cupped | 14 ( 7.0) |
| Visual field | |
| Mean deviation | |
| Mean (SD) | -13.26 (10.18) |
| Range | 0- -34 |
| Pattern standard deviation | |
| Mean (SD) | 5.33 (3.68) |
| Range | 7- 16 |
| Diagnosis at presentation | |
| PACS | 13 ( 6.5) |
| PAC | 52 (26.0) |
| PACG | 135(67.5) |
| Mild | 22 (16.3) |
| Moderate | 22 (16.3) |
| Advanced | 61 (45.2) |
| Absolute glaucoma | 30 (22.2) |
| Diagnosis based on laterality | |
| Bilateral PACS | 6 ( 3.0) |
| Bilateral PAC | 5 ( 2.5) |
| Bilateral PACG | 31 (31.0) |
| PACG and PAC | 13 (13.0) |
| PACG and PACS | 14 (14.0) |
| PAC and PACS | 31 (31.0) |
| Initial management | |
| Peripheral iridotomy/ iridectomy | 173 (86.5) |
| Topical antiglaucoma medications | 173 (86.5) |
| Beta-blockers | 146 (73.0) |
| Pilocarpine | 131 (65.5) |
| Prostaglandin analogues | 28 (14.0) |
| Dorzolamide | 30 (15.0) |

| Demographic data | N=100 |
|---|---|
| Subsequent management | |
| Lens extraction | 21 (10.5) |
| Trabeculectomy | 31 (15.5) |
| Non-augmented | 19 |
| Augmented | 12 |
| Progression | |
| No progression | 45 (22.5) |
| PACS to PAC | 28 (14.0) |
| PACS to PACG | 23 (11.5) |
| PAC to PACG | 38 (19.0) |
| Mild and moderate PACG to advanced PACG | 66 (33.0) |
| Duration of progression | |
| <6 months | 11 |
| 6 months to 1 year | 25 |
| 1 year to 2 years | 21 |
| >2 years | 55 |

CI 0.83, 0.96). The absence of peripheral iridotomy or iridectomy increased the risk of progression of 10 fold (95% CI 1.34, 74.95) (table III). The risk of progression was 16- and 4-times when diagnosis of PACG and PAC was made on the initial presentation, respectively (table III).

## DISCUSSION

Profound differences in clinical presentation and disease course of angle closure between Asians and Caucasians has led to the postulation that the disease is of two different entities[12]. Angle closure in Asians has been established to be more severe and accelerates faster when compared to Caucasians[13,12-13]. There are ample studies on angle closure among Chinese and Indians but only minimal knowledge is known among Malays[14-15]. Based on the present finding and literature reviews of previous studies [14-18], angle closure in Malays demonstrates an almost similar disease behavior as in other Asians population. However, this is an indirect comparison and subjected to other biases.

Chinese patients have a higher incidence of APAC and higher rate of admission based on retrospective observation in Singapore[8]. The incidence of APAC in Malays residing in Singapore was the lowest compared to Indian and Chinese[8]. Our findings have shown that APAC is common among Malays residing in Malaysia, with 47% found to have signs and symptoms of APAC. The different incidence between the two neighboring countries with almost similar culture is perhaps due to the difference in population distribution. However, our finding did not differ from other Asian populations. It is known that only 25 to 35% of angle closure in Asians is symptomatic[3,16- 16]. The incidences of APAC in our study were higher, which is likely to be due to overestimation. This is perhaps due to the retrospective nature of our study. APAC is usually associated with better awareness of the disease but it was not associated with protection against progression of the disease[20]. In fact, 66 eyes (33%) with APAC had shown progression to either PAC or PACG. However, APAC lost its significance as a predictor for progression in multivariate analysis.

**Table II: Comparison of clinical parameters between progress and non-progress eyes after at least 5 years of follow up**

| Clinical parameters | Progress N=112 | Non-progress N=88 | $X^2$ | p-value |
|---|---|---|---|---|
| Age at presentation | | | | |
| Mean (SD) | 61.42(8.35) | 61.44 (8.56) | | 0.984* |
| APAC | | | | |
| Yes | 66 | 28 | 14.54 | <0.001 |
| No | 46 | 60 | | |
| Symptomatic | | | | |
| Yes | 68 | 27 | 17.82 | <0.001 |
| No | 44 | 61 | | |
| Visual acuity | | | | |
| >6/7.5 | 16 | 13 | 12.06 | 0.034 |
| 6/9-6/12 | 26 | 31 | | |
| 6/15-6/24 | 13 | 13 | | |
| 6/30-6/48 | 9 | 9 | | |
| <6/60 | 41 | 13 | | |
| NPL | 7 | 7 | | |
| VCDR | | | | |
| 0.3-0.5 | 32 | 59 | 33.01 | <0.001 |
| 0.6-0.7 | 25 | 12 | | |
| 0.8-0.9 | 34 | 7 | | |
| Fully cupped | 8 | 6 | | |
| IOP (mmHg) | | | | |
| Mean (SD) | 38.9 (17.3) | 29.4 (18.7) | | <0.001* |
| MD | | | | |
| Mean (SD) | -18.70 (10.28) | -8.36 (7.21) | | <0.001* |
| PSD | | | | |
| Mean (SD) | 6.07 (4.15) | 4.67 (3.09) | | 0.060* |
| Diagnosis at presentation | | | | |
| PACS | 19 | 43 | 28.98 | <0.001 |
| PAC | 31 | 25 | | |
| PACG | 62 | 20 | | |
| Peripheral iridotomy/iridectomy | | | | |
| Yes | 91 | 82 | 6.01 | 0.014 |
| No | 21 | 6 | | |

NPL: non-perception to light
p-value <0.05 based on Pearson chi-square test and student t-test*

**Table III: Stepwise multiple logistic regression model on clinical predictors affecting progression of angle closure in Malays**

| Clinical predictors | Regression coefficient (b) | Adjusted OR for progression (a) 95% (CI) | Wald statistic | p-value |
|---|---|---|---|---|
| Age at presentation (years) | 0.19 | 1.02 (0.98, 1.06) | 5.20 | 0.021 |
| Visual field | | | | |
| MD | -0.12 | 0.89 (0.83,0.96) | 10.39 | 0.001 |
| Initial diagnosis at presentation | | | | |
| PACS | - | - | - | - |
| PAC | 1.31 | 3.71 (0.89, 15.45) | 3.26 | 0.071 |
| PACG | 2.78 | 16.15 (3.37, 77.42) | 12.10 | 0.001 |
| Peripheral iridotomy/iridectomy | | | | |
| Yes | - | - | - | - |
| No | 2.31 | 10.03 (1.34, 74.95) | 5.04 | 0.025 |

(a)Backward LR multiple logistic regression was applied. Multicollinearity and interaction term were checked and not found. The goodness of fit of this model was checked using the Hosmer-Lemenshow test; p=0.670. This result gives no evidence of lack of fit of the model.

As previously observed, progression to glaucomatous optic neuropathy was less in those with APAC when compared to asymptomatic and chronic disease[17]. Chronic and asymptomatic nature of angle closure among Malays is perhaps responsible for the higher incidences of Malay patients that presented with advanced optic neuropathy at initial presentation. 30 eyes (15%) were blind from PACG and 61 eyes (30.5%) were at an advanced stage of glaucoma on presentation. However, the impact of blindness in PACG among Malays was similar to Singaporean Chinese and Indians in Southern India[16-17]. Perhaps the problem of PACG related blindness in Southeast Asia is as big as in China, if proper prospective data was available among Malays on the Malay Archipelago. Lack of public awareness and 'old age is always associated with poor vision' attitude further contributed to late presentation and blindness[18]. High illiteracy rates among elderly in the Kelantan state of Malaysia may further worsen the situation[9].

The pathogenesis of angle closure in Asians is more complicated than in Caucasians. Multiple mechanisms that include thicker iris, pupillary block due to ocular biometry of Asian eyes, and non-pupillary block mechanisms such as the configuration of the iris are believed to increase the susceptibility to chronic angle closure in Asians[19]. Peripheral anterior synechecial closure (PAS) is believed to play a more significant role in the progression of disease. Asian eyes are more susceptible to the development of PAS due to ocular morphology and thicker iris[20]. However, the presence of PAS was not exponentially related to the incidence of PACG on initial presentation in our study. It is impossible to postulate or conclude the association of PAS with severity of PACG due to the retrospective nature of our study.

The majority of patients especially those with APAC received intensive medical treatment with systemic pressure lowering drugs, topical timolol, and pilocarpine to reduce IOP in preparation for laser peripheral iridotomy (LPI) or surgical iridectomy. LPI was found to be effective in breaking up the pupillary block in most Caucasian patients with APAC[21]. However, the outcome was not promising in Asian patients[22,23-24]. Peripheral iridotomy or surgical iridectomy conferred a limited protective effect against progression of angle closure. The risk of progression was found to be 10 fold (95% CI 1.34, 74.95) in eyes without peripheral iridotomy/iridectomy based on a multivariate analysis. In spite of postulated protective effect, 91(45.5%) eyes still progressed even with patent peripheral iridotomy/iridectomy. A randomized control trial of prophylactic laser peripheral iridotomy in high risk eye of PAC eyes in Mongolian population, failed to prevent the progression to PACG[25]. There was no significant difference in progression to PACG between those who received prophylactic LPI and those without LPI after 6 years of prospective follow up[27]. Aggressive intraocular pressure (IOP) reduction to more than 30% by medical treatment and earlier LPI conducted within 7 days after initial presentation APAC was associated with better IOP reduction in patients with APAC[26-27]. LPI is slightly difficult to perform in Asians with thicker and highly pigmented irides and is associated with more complications when compared to Caucasians.

Subsequently, cataract extraction was conducted in 21 eyes and trabeculectomies were performed in 31 eyes. Cataract extraction has been found to widen the narrow angle, deepen the anterior chamber, and attenuate the anterior positioning of ciliary processes in PAC; thereby, relieving pupillary block and lower the pressure in PAC[28]. The benefit of lens extraction was not established well during the management of most of the recruited patients in our retrospective study. This is due to small numbers of eyes that have undergone cataract extraction during the retrospective review of this study. In fact, currently randomized control trials on the benefit of clear lens extraction in ACG patients are on-going[29].

After at least 5 years of follow up, 112 eyes progressed in spite of vigilant follow up and treatment. We reported lower incidences (14%) of progression from PACS to PAC when compared to a prospective study on the Indian population (28%)[30]. The difference could be due to the differences in the methodology. A prospective study may provide more accurate outcomes rather than studies that are retrospective in nature. Alarmingly, there were cases of PACS that converted to PACG (23 eyes, 11.5%) within at least 5 years of follow up. Unlike reports in the Indian population, LPI does not confer protective effects against the progression or changes in the course of the disease for Malays[22, 28]. The initial diagnosis of PAC increased the risk of progression to 4-fold (95% CI 0.89, 15.45). Once glaucomatous damage has set in, the chances for further progression escalated 4-times to 16-fold (95% CI 3.37, 77.42). Thus, suggesting that more aggressive treatment is needed to halt or slow the progress of angle closure in Malays. However, to conclude that Malays progressed faster in angle closure is inappropriate due to the retrospective nature of this study. Higher IOP during follow up was found to increase the risk of progression in Asian populations [7, 32]. Aggressive reduction of IOP of less than 22mmHg was found to reduce risks of progression in Asians7. Perhaps, there are other factors responsible for acceleration of the disease such as genetic, vascular, or environmental factors.

Age has been identified as strong risk factor for glaucoma development. It is no surprise that increasing age was associated with increased risk of progression, for every 1 year increase in age conferred 1 fold risk of progression (95% CI 0.98, 1.06) in Malays. Reduction of severity in HVF was associated with protection against progression. Higher IOP at presentation was associated with the progression in univariate analysis but lost its effect in multivariate model.

A better preventive and treatment strategy should be addressed to prevent progression of angle closure glaucoma in Malay population in Malaysia. Effective health awareness campaign should be formulated addressing the custom and culture of Malay population especially in rural area. Extended family unit is widely practiced among Malays in Kelantan. Identifying and educating the decision maker in the family will be more effective. Vigilant follow up and aggressive treatment including cataract extraction may help in reducing the IOP in angle closure patients preventing progression to glaucomatous optic neuropathy.

## CONCLUSION

The incidence of angle closure in Malays is more common than previously reported. The clinical presentation, severity, and progression of angle closure glaucoma in Malays are similar to other Asian populations based on indirect comparison. Underestimation is more likely in this retrospective study. It is important to strategize preventive measures in Asians without neglecting the Malay population. Vigilant follow up and aggressive pressure lowering may help in the prevention of progression in Malays.

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