EVALUATION OF ANTERIOR SEGMENT BIOMETRY PARAMETERS IN PROGRESS AND NON-PROGRESS PRIMARY ANGLE CLOSURE GLAUCOMA AMONG MALAYS AND CHINESE

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DISCLAIMER

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ABSTRAK

Latar Belakang

Glaukoma sudut tutup primer merupakan glaukoma yang kedua lazim ditemui di Asia dan merupakan punca utama kebutaan disebabkan oleh glaucoma. Di kalangan Asian, Glaukoma sudut tutup primer dipercayai progres lebih cepat. Identifikasi pesakit-pesakit yang berisiko untuk progress cepat adalah penting untuk mengurangkan morbiditi dan beban penyakit. Kebanyakan pengetahuan tentang beban, risiko dan epidermiologi tentang glaukoma sudut tutup primer diperolehi dari populasi risiko tinggi, misalnya Cina, Jepun dan India. Di Malaysia, majoriti populasi terdiri daripada kaum Melayu dan Cina. Perbezaan antara etnik mungkin mempengaruhi tahap progres glaukoma sudut tutup primer. Golongan Melayu telah didapati untuk mempunyai penglihatan lebih teruk dan progres pada kadar yang lebih teruk kalau berbanding dengan golongan Cina di Malaysia pada masa presentasi penyakit. Parameter-parameter biometri segment hadapan mata seperti “axial length” telah diketahui mempunyai perkaitan rapat dengan progres glaukoma sudut tutup primer ke tahap yang lebih teruk. Dengan ini, kami akan menyiasat parameter-parameter ini di kalangan Melayu dan membuat perbandingan antara parameter-parameter ini antara dua etnik major di Malaysia.

Objektif:

Untuk membuat perbandingan parameter-parameter biometri segment hadapan mata di antara pesakit Melayu dan pesakit Cina glaukoma sudut tutup primer yang progress dengan pesakit yang tidak progress.

Kaedah Kajian:

Ini merupakan satu kajian rentas yang melibatkan 75 pesakit (43 pesakit Melayu glaukoma sudut tutup primer dan 32 pesakit Cina glaukoma sudut tutup primer. Pesakit-pesakit ini

direkruit dari satu pusat glaukoma di Malaysia antara November 2015 hingga Disember 2016. Pemeriksaan mata termasuk pengukuran “axial length (AL)” dan “anterior chamber depth (ACD)” dengan menggunakan satu alat “non-contact partial coherence inferometer (IOL Master, Carl Zeiss, Germany). Manakala, “anterior chamber angle (ACA)” diukur dengan “Anterior Segment-OCT (Spectralis Heidelberg, Germany). Keluasan pandangan pada mata yang sama dijalankan dengan analisis “Humphrey visual field (HVF) 24-2” untuk mengkaji tahap progresi glaukoma pesakit. Pesakit-pesakit dikategorikan kepada dua kumpulan iaitu kumpulan yang dengan progresi dan kumpulan yang tanpa progresi. Perbandingan parameter-parameter biometri segment hadapan mata antara pesakit Melayu dan pesakit Cina glaukoma sudut tutup primer yang progres dan tanpa progresi telah dianalisis dengan “independent T test” dan “multivariate ANOVA”.

Keputusan:

Pesakit Cina glaukoma sudut tutup primer mempunyai “AL” yang lebih pendek (22.18mm±0.76) dan “ACA” yang lebih sempit (11.09°±1.31) berbanding dengan pesakit Melayu. Tetapi, perbandingan di antara “ACD” di antara pesakit glaukoma sudut tutup primer Melayu dan Cina didapati tiada perbezaan yang signifikasi. Selepas penyelarasan untuk faktor membaurkan, hanya “ACA” didapati ada perbezaan signifikasi. Di kalangan pesakit yang progres, semua parameter-parameter (“AL”, “ACD”, “ACA”) didapati mempunyai perbezaan ynag signifikasi di antara Melayu dan Cina. Tetapi elepas penyelarasan untuk faktor membaurkan, semua parameter tiada perbezaan yang signifikasi. Walau bagaimanapun, dalam kumpulan tanpa progress, tiada perbezaan yang signifikasi dalam parameter-parameter biometri segment hadapan didapati di antara dua kumpulan etnik ini. Pesakit Melayu glaukoma sudut tutup primer yang progres mempunyai “ACA” yang lebih sempit (11.96°±6.00)

berbanding dengan pesakit yang tidak progres. “AL” dan “ACD” antara pesakit Melayu glaukoma sudut tutup primer yang progres dan tanpa progres tidak berbeza secara signifikan.

Kesimpulan

Parameter-paramter biometri segment hadapan mata dipengaruhi oleh faktor eknik Kaum Cina mempunyai “ACA” yang lebih sempit berbanding dengan kaum Melayu. Serial Pemantauan dengan “Anterior Segment-OCT” adalah penting dalam rawatan glaukoma sudut tutup primer. Pemeriksaan parameter-paramter biometri segment hadapan mata adalah penting dalam menjangka risiko progress di kalangan kaum Melayu. Penyelidikan yang seterusnya diperlukan sebelum kami boleh membuat kesimpulan tentang perkaitan di antara parameter-parameter biometri sudut hadapan mata dengan progress glaukoma sudut tutup primer.

ABSTRACT

Background:

Primary angle closure glaucoma (PACG) is the second most common type of glaucoma in Asia, and the main cause of glaucoma blindness. PACG is believed to progress faster among Asians. Identification of patients at risk of progression is crucial to reduce the morbidity and disease burden. Most knowledge of burden, risk factors and epidemiology about PACG has been derived from high risk populations such as Chinese, Japanese and Indians populations. Both Malay and Chinese comprise the majority population in Malaysia. Ethnic differences in PACG progression may exist; Malays have been found to present with worst visual acuity and progression compared to Chinese residing in Malaysia. Anterior segment biometry parameters such as axial length have been associated with progression of PACG. As anterior segment biometry has been found to be associated with progression, we aimed to investigate these parameters in Malays and to.compare these parameters between the two major ethnicity in Malaysia.

Objective:

The aim of this study were to compare anterior segment biometry parameters in progress and non-progress PACG among Malays and Chinese.

Methods:

This was a cross-sectional study involving 75 patients (43 Malay PACG patients and 32 Chinese PACG patients) recruited from 1 glaucoma centre in Malaysia recruited between November 2015 and December 2016. Ocular examination included axial length (AL) and anterior chamber depth (ACD) measurement using a noncontact partial coherence interferometer (IOL Master, Carl Zeiss, Germany). Anterior chamber angle (ACA), measured

by Anterior Segment-OCT (Cirrus, Carl Zeiss, Germany). Humphrey visual field (HVF) 24-2 analysis of the same eye was done and used to evaluate glaucoma progression. Patients were categorized into two groups: those with progression and those without. Comparison of anterior segment biometry parameters between Malay and Chinese PACG patients with and without progression was analysed using independent T test and multivariate ANOVA analysis.

Results:

Chinese PACG patients had shorter AL (22.18mm±0.76) and narrower ACA (11.09°±1.31) than Malay PACG patients. There was no significant difference between the ACD of Malay and Chinese PACG patients. After adjustment for confounding factors., only ACA was significantly difference. Among patients with progression, all the anterior segment biometry parameters (AL, ACD, ACA) were significantly different between Malays and Chinese. However, after controlling for confounding factors, there was no significant difference, In the group without progression, no significant differences in anterior segment biometry parameters were observed between the two ethnic groups. Malay PACG patients with progression had narrower Anterior Chamber Angle (ACA) (11.96°±6.00) compared to non-progressing patients. Axial Length (AL) and Anterior Chamber Depth (ACD) did not differ significantly between Malay patients with and without progression.

Conclusion:

There was racial influence in ocular biometry measurement in PACG patients. Chinese has significant narrower ACA compared to Malays. Serial AS-OCT monitoring is important in management of PACG. Evaluating anterior segment biometry parameters is essential in predicting risk of progression in Malay PACG. Further researches and larger studies need to

be conducted before we can further conclude the association of the anterior segment biometry parameters with progression of PACG.

Chapter 1
Introduction

1.1 PRIMARY ANGLE-CLOSURE GLAUCOMA (PACG)

PACG is the major form of glaucoma in Asia, and late presentation has been shown as the major contributory factor for blindness (Chen, 2004). PACG is characterized as a chronic, progressive visual field loss and optic nerve cupping, often associated with an elevated intraocular pressure (IOP) due to the presence of iridotrabecular contact (ITC) by gonioscopy, which can either be appositional or synechial, in the absence of underlying secondary ocular disease ("European Glaucoma Society," 2014). The rise in IOP is a result of poor aqueous outflow through the trabecular meshwork because of the ITC leading to a build-up in aqueous within the eye, hence increased in IOP (Niwas *et al.*, 2016). Typical symptoms of PACG especially if they have an Acute primary angle closure (APAC) include eye pain, frontal headache on the side of affected eye, nausea and vomiting, “halos” around lights at night, and very blurred vision ("European Glaucoma Society," 2014; "Glaucoma Research Foundation," 2012). However, majority of those with PACG presents as a chronic, asymptomatic form while the acute, symptomatic ones are seen in less than 25% of cases (Foster *et al.*, 2002; Quigley, 2011).

The current classification of PACG is based on clinical observations in European populations and can be classified into three types; Primary angle closure suspect (PACS), Primary angle closure (PAC) and PACG. PACS is defined as an eye in which 180^{o} or more appositional contact between the peripheral iris and posterior trabecular meshwork is considered possible with normal IOP, no peripheral anterior synechiae (PAS) and no evidence of glaucomatous optic neuropathy (GON). PAC is defined as an eye with 180^{o} or more occludable drainage angle and features indication that trabecular obstruction by the peripheral iris has occurred, such as raised IOP of more than 21 mmHg, PAS, iris whirling, “glaucomflecken” lens opacities, or excessive pigment deposition on the trabecular surface in the absence of GON.

The term PACG is used to indicate PAC eyes with GON ("European Glaucoma Society," 2014; Foster *et al.*, 2002).

PACG has a relatively higher prevalence and tends to be asymptomatic in East Asians (He *et al.*, 2006a). Compared to eyes with previous history of symptomatic angle closure, asymptomatic PACG was noted to carry poorer visual outcome as they usually present with severe to end-stage visual field loss at first presentation to hospital. (Ang *et al.*, 2004b).

1.1.1 Prevalence of PACG in Malay & Chinese population

Glaucoma is the second leading cause of blindness worldwide, following cataract (Quigley, 1996; Thylefors *et al.*, 1995). WHO has estimated that 4.5 million people are blind due to glaucoma (Quigley and Broman, 2006). It also projects that nearly half of the bilateral blindness attributable to glaucoma by 2020 will be caused by angle closure glaucoma, in which Asians will represent 87% of those with PACG (Quigley and Broman, 2006). In Malaysia, glaucoma emerged as the fifth leading cause of both blindness and low vision based on the National Eye Survey 1996 (Zainal *et al.*, 2002). This represents to roughly 1.8% of all bilateral blindness and 1.8% of all low vision in our country's population (Zainal *et al.*, 2002).

Asia constitutes for a disproportionately higher prevalence of PACG (Quigley, 1996). Based on the prevalence models by Quigley and Broman (2006), in 2010 higher prevalence of PACG cases are seen in Asian countries; China 1.26%, Southeast Asia 1.20%, India 0.80%, as compared to the lower prevalence seen in other parts of the world; Europe 0.25%, Latin America 0.19%, Africa 0.16% (Quigley and Broman, 2006). An exception to Japan and Middle East which registered a lower than average prevalence of 0.39% and 0.16% respectively

(Quigley and Broman, 2006). Therefore, Asians represents 87% of the 15.7 million with ACG (Quigley and Broman, 2006).

Ethnic or geographic differences in the prevalence rates of PACG are well known, with relatively high prevalence rates (1.1%-2.0%) in Chinese, Mongolian, and Singaporean Chinese (Sawaguchi *et al.*, 2012). Studies show that the Chinese population is one of the most at risk for developing PACG (Hu, 1989b). It is estimated that 3.5 million people in China have PACG and 28 million have narrow anterior chamber angles (Foster and Johnson, 2001).

The Malay race accounts for 5% of the world's population. Despite there are approximately 300 million to 400 million people of Malay ethnicity living in Asia ("Population Reference Bureau ", 2016), the burden, causes, risk factors and epidemiology of blinding eye diseases in this ethnic group are not well studied.

Based on the data released by the Department of Statistics, Malaysia, the population of Malaysia was 28,334,135, making it the 42nd most populated country. Malaysia is a heterogenous population with many races, of which Chinese and Malays predominate. Based on the National Consensus 2010, Malays make up 61.9% of the population followed by Chinese (22.5%) and Indians (6.7%) (Department of Statistics, 2010).

The prevalence of PACG in Malays was 0.12% based on the Singapore Malay Eye Study (SiMES) that involved 3280 participants aged 40 to 80 years (Shen *et al.*, 2008). Interestingly, although PACG is often associated with Chinese ethnicity, in a retrospective study of chronic angle closure glaucoma in Malaysia, Taiwan, and Hong Kong found that the progression rate of PACG was higher in Malays when compared to Chinese (Sharmini *et al.*, 2009). Another

publication by Sharmini AT, et al in 2014 on Malay patients with PACG found that Malay PACG patients have the risk of progression up to 16-fold (Liza-Sharmini *et al.*, 2014). A genome wide association study showed susceptibility loci associated with PACG, suggesting that genetic development of the eye in different races may be a contributory factor in the pathogenesis of PACG (Vithana *et al.*, 2012).

1.1.2 Risk Factors for Primary Angle Closure Glaucoma

It is essential to acknowledge the range of factors that affect its progression due to its blinding potential. The risk factors can be divided into non-modifiable and modifiable risk factors.

Non-Modifiable Risk Factors

Age

Advancing age is a known risk factor for developing PACG (Stephen and Drance, 1997). Numerous population-based prevalence studies carried out globally supported this. A study about prevalence of PACG in a rural southern Indian population showed that the odds for PAC and PACG increased with age after adjusting for sex. The odds ratio (OR) increased from 2.34 (95% CI, 1.14 to 4.79) for the age group of 50 to 59 years to 3.95 (95% CI, 1.81 to 8.61) for the subjects aged 70 years or older (Vijaya *et al.*, 2006). In a rural northern China, study found the prevalence of PACG for the age group 40 to 49 was 0.63% (95% CI, 0.24 to 1.01) and increased to 2.97% (95% CI, 1.72 to 4.23) for those 70 years and above (Song *et al.*, 2011). This was seconded by another study on rural and urban northern China population (Wang *et al.*, 2010).

In Malaysia alone, it was reported that Malays, for each year increase in age increases the risk of disease progression with an odd ratio of 1.02 (95% CI, 0.98 to 1.06) (Liza-Sharmini *et al.*, 2014). Meanwhile, regional studies in Singapore (Baskaran *et al.*, 2015; Foster *et al.*, 2000c), India (Dandona *et al.*, 2000), Europe (Bonomi *et al.*, 2000) and Africa (Buhrmann *et al.*, 2000) also supported age as a risk factor for PACG. The incidence of PACG is expected to rise with the growth of elderly population in view of accessibility and availability of better health care system.

Race

A genome wide association study showed susceptibility loci associated with PACG, suggesting that genetic development of the eye in different races may be a contributory factor in the pathogenesis of PACG (Vithana *et al.*, 2012). Numerous large population-based studies, the disproportionate prevalence of glaucoma among races indicated that race and ethnicity might play an important role as a risk factor in PACG. The highest prevalence rates are seen in Inuit ranging from 2-4% (Alsbirk, 1973; Arkell *et al.*, 1987; Rens *et al.*, 1988). Relatively high prevalence rates (1.1%-2.0%) in Chinese, Mongolian, and Singaporean Chinese (Sawaguchi *et al.*, 2012). Studies show that the Chinese population is one of the most at risk for developing PACG (Hu, 1989b).

PACG is approximately three times more common in Asians (predominantly Mongolian and Chinese population) compared to European-derived populations (He *et al.*, 2006a). Contrary, the prevalence reported in the western countries are much lower. For example, in the Blue Mountains Eye Study, the prevalence of PACG in Australia was 0.3% (Mitchell *et al.*, 1996); in northern Italy with 4,297 study participants, PACG was reported in 0.6% of the patients

(Bonomi *et al.*, 2000); among Americans in the Beaver Dam Eye Study, the prevalence for PACG was 0.04% (Klein *et al.*, 1992).

A meta-analysis of 29 published studies on Asian populations suggested a strong association of prevalence with ethnic group through meta-regression analysis ($\beta = 0.27$, $p = 0.009$) (Cheng *et al.*, 2014).

Sex

Gender differences in the prevalence of PACG has been well documented in numerous population-based prevalence studies (Lai *et al.*, 2001; Liza-Sharmini *et al.*, 2014; Shen *et al.*, 2008; Song *et al.*, 2011; Vijaya *et al.*, 2006; Wang *et al.*, 2010).

A meta-analysis of 29 published studies on Asian populations, with data from 84,079 subjects with PACG reported prevalence was 0.63% for male and 0.91% for female. A meta-regression analysis showed a strong association between a high prevalence rate and a higher proportion of female gender ($\beta = 0.41$, $p = 0.047$). The overall female to male ratio of the PACG prevalence was 1.51:1 (95% CI, 1.01 to 2.28) (Cheng *et al.*, 2014).

Family history and genetics

Glaucoma is a complex disease, both clinically and genetically. A positive family history of PACG is an additional risk factor. The inheritance of PACG is believed to be polygenic (Alsbirk, 1982; Lowe, 1970; Wilensky *et al.*, 1993), although both autosomal dominant and recessive inheritance pattern are seen in pedigrees with high a prevalence of PACG.

A study on Chinese population found that the disease prevalence among first-degree relatives of PACG patients, only parents account for an odd ratio of 8.76 (95% CI, 2.00 to 38.32) (Kong *et al.*, 2011). A high heritability of narrow angles of almost 60% was found. It has also been observed that siblings of patients with angle closure have substantially higher risk of angle closure as compared to siblings of individual with open angles. The estimated odds of angle closure 21.1 times higher (95% CI, 2.8 to 160.1) among siblings of PACS, PAC or PACG (Venkatesh *et al.*, 2012). A high heritability of narrow angles of almost 60% was found (Amerasinghe *et al.*, 2011). Siblings of Chinese patients with PAC or PACG have almost a 50% probability of having narrow angles and are more than 7 times more likely to have narrow angles than the general population (Amerasinghe *et al.*, 2011).

Visthana EN et al, conducted a genome-wide association study on PACG with 3,771 PACG cases and 18,551 controls, and identified 3 strongly associated genetic variants: rs11024102 in PLEKHA7; rs3753841 in COL11A1 and rs1015213 located between PCMTD1 and ST18 on Chromosome 8q (Vithana *et al.*, 2012). However, these 3 sequence variants only account for less than 2 percent of PACG risk (Vithana *et al.*, 2012). A recent study by Nongpiur ME et al, identified a common genetic variant within ABCC5 with a significant association with anterior chamber depth, which was also associated with a modest risk for PACG (Nongpiur *et al.*, 2014).

Ocular biometry

Related studies on biometrical comparisons between normal eyes and eyes with PACG showed that PACG eyes are smaller in axial length (AL), have flatter corneas, shallower anterior chamber depth (ACD) and thicker lenses (Lowe, 1970; Marchini *et al.*, 1998; Sihota *et al.*, 2008). Eyes with shorter AL will tend to have thicker lenses sited more forward. Patient with PACG was found to have ACD that is 1.0 mm shallow than non-disease eyes, of which, 0.65

mm of shallowing attributed by the whole lens being anteriorly positioned and 0.35 mm by increased in lens thickness (Lowe, 1970).

Obviously, smaller ocular biometry is a risk factor for PACG, but the differences among ethnicity in AL and ACD are not substantial enough to explain the increase of angle closure in Chinese population. It only means small eyes among the Chinese are more likely to develop PACG than small eyes among other ethnicity. Therefore, it is unlikely that a single risk factor will fully explain the inter-racial predisposition towards angle closure (He *et al.*, 2006a; Quigley *et al.*, 2003). With the widely availability and accessibility to Anterior Segment Optical Coherence Tomography (AS-OCT), various studies start to focus anterior segment biometry evaluation instead of ocular biometry alone. Nevertheless, the data on the associated of anterior segment biometry still very limited. Hence, we will emphasize on anterior segment biometry parameters with the association of progression of PACG. Detailed discussion and elaboration on the anterior segment biometry parameters will be further discussed.

Modifiable Risk Factors

Intraocular pressure (IOP)

IOP is the pressure that established when equilibrium between production and outflow of aqueous is achieved. “Normal” IOP is defined as 2 standard deviations above or below the mean IOP, thus giving a range between 10 to 21 mmHg. IOP that is outside this range is considered abnormal (Alimuddin, 1956). IOP has a strong correlation with the progression of glaucoma. It is evidenced by a strong correlation between pre-treatment IOP and the extent of visual field loss in PACG for both MD and AGIS (Gazzard *et al.*, 2003). Conventionally, IOP is considered as a major and only modifiable risk factor in glaucoma progression. Given that

IOP is the only modifiable risk, many authors have been in search for solutions for controlling IOP. It remains a challenging task as IOP itself is affected by various factors including environmental factor. Hence, many hypothesis of modifiable risk factors that strongly associate with IOP have been proposed. These includes: physical activity (Williams, 2009), cigarette smoking (Chiotoroiu *et al.*, 2013; Jain *et al.*, 2016), body mass index (BMI) (Berdahl *et al.*, 2012; Pasquale and Kang, 2009), mean arterial blood pressure (Klein *et al.*, 2005; Werne *et al.*, 2008), caffeine (Chandrasekaran *et al.*, 2005; Pasquale and Kang, 2009) and alcohol intake (Chiotoroiu *et al.*, 2013; Klein *et al.*, 1993).

1.2 PROGRESSION IN PACG

1.2.1 Definition of progression

The most common method used to quantify glaucomatous damage is using serial HVF evaluation (Brusini and Johnson, 2007). At baseline, it detects and quantifies damage, and in subsequent follow-up of a glaucoma patient, it detects stability or progression of the disease over a period of time (Susanna Jr and Vessani, 2009). To quantify the severity of glaucomatous damage using analysis of structural damage to the ONH and RNFL is still under evaluation (Brusini and Johnson, 2007).

Progression of glaucoma can be evaluated either structurally or functionally, or both. In current practice, monitoring of disease progression is done using serial evaluation of longitudinal series of visual field (functional) measurements (Kirwan *et al.*, 2014; Saunders *et al.*, 2014). It can also be used to detect early glaucoma damage (Giangiacomo *et al.*, 2006). Standard automated perimetry (SAP) is the most common method for assessing VF in glaucoma and has been widely used for many years (Chauhan *et al.*, 2008). It is a recommended measure by The

European Glaucoma Society for monitoring rate of VF progression in our daily clinical practice ("European Glaucoma Society," 2014). As in our context, VF progression is the preferred method because in view of the reason mentioned above.

Furthermore, the evaluation of visual field progression can be achieved by employing trend analysis and event-based analysis (Diaz-Aleman *et al.*, 2009; Spry and Johnson, 2002).

Trend Analysis

Trend analysis uses mean deviation index (MDI) or visual field index (VFI) calculated from the Humphrey visual field (HVF) perimetry, has become a standard index for estimating the progression rate of glaucoma (Casas-Llera *et al.*, 2009). Nonetheless, MDI calculation correlate poorly with clinical findings (Arnalich-Montiel *et al.*, 2009) because it can be influenced not only by increasing glaucoma progression and severity, but also the presence of any media opacities such as cataract. Thus, progressive increase in cataract density can falsely be mistaken as high glaucoma progression rate (Klein *et al.*, 1996; Koucheki *et al.*, 2004).

The value of MDI will improve after cataract extraction and this may further interfere with the evaluation and monitoring of glaucoma progression (Klein *et al.*, 1996; Koucheki *et al.*, 2004). Another limitation of using MDI is that it is very weakly centre weighted, therefore it does not correlate well to patient's real visual function (Heijl *et al.*, 1987).

Event-based Analysis

The event-based analysis is essentially to detect whether progression has occurred or not (Caprioli, 2008). Glaucoma progression analysis (GPA) software incorporated in Humphrey Visual Field Analyser (HVA) (Carl-Zeiss Meditec, Dublin, CA) is an example of event-based

analysis (Casas-Llera *et al.*, 2009). The software will give an analysis of pattern standard deviation (PSD) values (Casas-Llera *et al.*, 2009) allowing for glaucoma progression monitoring. Recently, glaucoma progression index (GPI) was introduced to measure the rate of VF progression (Bengtsson and Heijl, 2008). GPI is based largely on PSD analysis but is displayed in the form of linear regression (Bengtsson and Heijl, 2008; Casas-Llera *et al.*, 2009). It was found that GPI analysis is more accurate than the traditional MDI analysis for determining rate of progression and is considerably less affected by cataract or cataract surgery (Bengtsson and Heijl, 2008).

The event-based GPA analysis is capable of detecting progression earlier compared to trend VFI analysis by 7 months (Casas-Llera *et al.*, 2009). Trend-based analysis requires larger number of HVF test to detect progression (Caprioli, 2008). A primary limitation of event-based analysis is in detecting progression of defect in the central 10 degrees (Arnalich-Montiel *et al.*, 2009; Diaz-Aleman *et al.*, 2009).

Various staging systems using SAP have been proposed such as Hodapp-Parrish-Anderson (HPA) classification (Hodapp *et al.*, 1993); Glaucoma Staging System (GSS) (Brusini, 1995); Advanced Glaucoma Intervention Study (AGIS) (Investigators, 1994) etc.
We used HPA classification because this is a clinically useful method, and is currently the classification system most commonly used in clinical studies (Brusini and Johnson, 2007; Hodapp *et al.*, 1993).

Hodapp-Parrish-Anderson (HPA) classification

HPA classification system considers two criteria: the first criterion is the overall extent of damage using both the mean deviation (MD) value and the number of defective points in the

Humphrey Statpac-2 pattern deviation probability map of the 24-2, SITA-STANDARD test; the second is based on the defect(s) proximity to the fixation point (Susanna Jr and Vessani, 2009). This classification, though popular has its own disadvantages, namely the visual field defect is characterized into four relatively course stages and does not give information about the location and depth of the defect(s). It may also be impractical in everyday practice because it requires time-consuming analysis of every VF test results. Another limitation is this system may suggest a significant deterioration when in fact none has occurred (Susanna Jr and Vessani, 2009)

According to HPA classification, VF progression is based on:

1. New defects

    a) 3 or more non-edge points are depressed > 5dB or $p < 5\%$
    b) 1 non-edge points are depressed >10dB

2. Deeping defects

    a) 3 or more non-edge points are depressed >10dB
    b) May be different if contiguous

3. Expanding scotoma

    a) 2 points within central 15 degree or 3 points outside central 15 degree are depressed >10dB or $p>5\%$.

1.2.2 Factors affecting progression of PACG

Same as risk factors for PACG, factors affecting progression of can be divided into non-modifiable and modifiable risk factors.

Recently emerging research indicates that modifiable risk factors other than

IOP may be associated with the presence and/or progression of glaucoma (Boland and Quigley, 2007; Chang *et al.*, 2010; de Voogd *et al.*, 2006; Garg *et al.*, 2014; Werne *et al.*, 2008). A systemic review on assessment of risk factors for the progression of glaucoma based on several clinical trials, population-based cohort studies and large retrospective studies had been done (Friedman *et al.*, 2004). They summarized the risk factors for progression of glaucoma includes:

(i) Age (*AGIS; Collaborative Initial Glaucoma Treatment Study, (CIGTS); Early Manifest Glaucoma Trial (EMGT)*)

(ii) Diabetes mellitus (*AGIS; CIGTS*)

(iii) Disc haemorrhage (*Collaborative Normal Tension Glaucoma Study (CNTGS); EMGT*)

(iii) female (*CNTGS*) or male (*AGIS*)

(iv) higher IOP at the onset (*EMGT*)

(v) higher IOP over the follow up (*CNTGS; EMGT*)

(vi) race as in African (*CIGTS*); Asian (*CNTGS*)

(vi) baseline visual field (*EMGT*).

Of all the risk factors mentioned above, diabetes mellitus and the IOP were the only modifiable risk factors (Friedman *et al.*, 2004).

There various other hypothesized risk factors includes glaucoma family history (Tielsch *et al.*, 1991), body mass index (BMI) (Berdahl *et al.*, 2012; Pasquale and Kang, 2009), mean arterial blood pressure (Werne *et al.*, 2008), physical activity (Williams, 2009), cigarette smoking (Bonovas *et al.*, 2004; Chiotoroiu *et al.*, 2013; Wang *et al.*, 2012), caffeine (Chandrasekaran *et al.*, 2005; Pasquale and Kang, 2009) and alcohol intake (Chiotoroiu *et al.*, 2013; Klein *et al.*, 1993).

1.3 ANTERIOR SEGMENT BIOMETRY PARAMETERS IN PACG PATIENTS

Various contact and non-contact techniques have been utilized to evaluating the risks of progression in PACG. Gonioscopy is the clinical reference standard for evaluating the angle and detecting angle closure. Unfortunately, it is subjective and requires considerable skills and experience for accuracy. Less invasive methods of assessing the anterior segment including ultrasound biomicroscopy (UBM), Scheimpflug Photography (Pentacam) and Anterior Segment Optical Coherence Tomography (AS-OCT) have been gaining in popularity, especially as they provide quantitative, reproducible data (Reetika S *et al*).

AS-OCT is a non-contact method that provides cross-sectional, three-dimensional, high-resolution images using low coherence interferometry to achieve axial resolution in the range of 3–20 μm. It allows cross-sectional imaging of anterior segment structures. Apart from this, it provides qualitative and quantitative assessment of the anterior segment structures important to the pathogenesis and the anatomical variations of glaucoma, and the approach to and success of treatment (*Reetika S et al*).

Optical coherence tomography (OCT) was invented by David Huang and colleagues in 1991. Anterior segment imaging using OCT was first demonstrated in 1994 by Izatt et al using light with a wavelength of 830 μm. Later, Lubech's group described OCT imaging of laser thermokeratoplasty lesions in 1997, and Maldonado and colleagues reported imaging of LASIK flaps in 1998. Huang and Izatt in 2001 first demonstrated the modern version of anterior segment OCT using 1,310 nm wavelength light and a scan speed of 4000 A-scans/sec, with telecentric transverse scanning and rapid scanning optical delay technology in a reference arm yielding an axial resolution of 17 μm. Subsequently, the development of spectral domain OCT (SD-OCT) came in to place. AS-OCT has been shown to offer precise anterior chamber angle

(ACA) measurements and to detect more closed angles than gonioscopy (Nolan WP, *et al,* 2007).

Biometric studies have demonstrated a few parameters associated with progression of PACG. Eyes with acute primary angle closure glaucoma (APACG) have shallower anterior chambers (Lowe, 1970; Seah *et al.*, 1997; Wong *et al.*, 2000) and shorter axial lengths (AL) (Foster, 2002; Lowe, 1970; Seah *et al.*, 1997; Wong *et al.*, 2000) than controls.

1.3.1 Axial length (AL) and PACG

Axial length (AL) is the distance from the posterior corneal surface to an interference peak corresponding to retinal pigment epithelium/Bruch's membrane (Hitzenberger, 1991). AL is made up from Anterior Chamber Depth (ACD) + Lens Thickness (LT) + Vitreous Cavity Length (VL) (Figure 1)

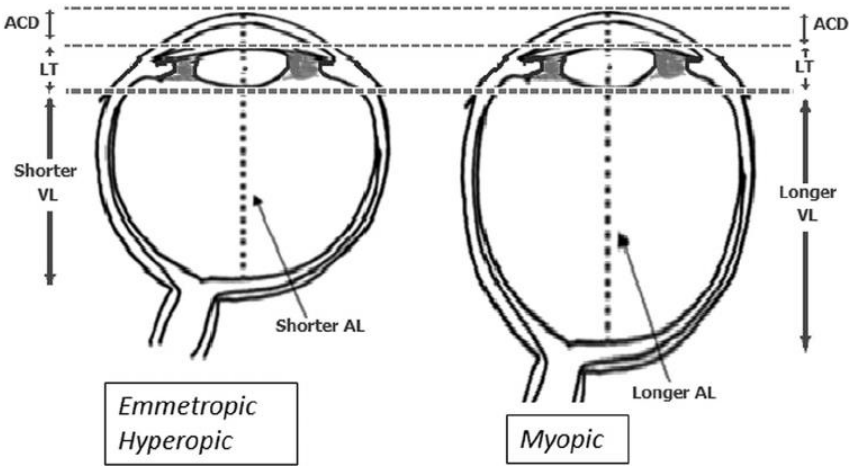


Figure 1: Illustration shows the relation of ACD, LT, VL and AL (Adapted from Myopia in Asian Subjects with Primary Angle Closure by *Kai-Ling Yong* et al, 2014) (Yong *et al.*, 2014)

The IOL Master optical biometry system (Carl Zeiss Meditec, AG), and its partial coherence interferometry prototypes, have been extensively studied for AL measurement determination for the calculation of IOL power. This technology has been shown to have excellent reliability and performance accuracy that is, at a minimum, comparable to those of immersion ultrasound and significantly better than applanation ultrasound. This is because optical biometry achieves accuracy within 20 μm (ultrasound is accurate to 100 μm), thus refractive errors stemming from AL mismeasurement are limited to 0.05 diopter (D), which translates to a 5 times more accurate measurement than that obtainable by ultrasound (*Warren H et al, 2008*).

The IOL Master is widely use to aid the accurate calculation and selection of IOL in cataract surgery worldwide. The IOL Master measures AL, anterior corneal radii, ACD, and the white-to-white distance in the human eye. Axial length measurement acquisition failure with the IOL Master has been reported in the literature. Causes have been attributed to an inability to position the patient at the instrument (eg, head tremor), a combination of low vision and lens opacity, and fixation difficulties due to macular disease. Dense nuclear cataracts and posterior subcapsular cataracts appear to be the most common reported cause of AL measurement acquisition failure. However this had no limitation in our study as those patients were coincidentally excluded from our study according to the inclusion and exclusion criteria for our study subjects selection. With the proven reliability of IOL Master in obtaining AL, it was the chosen technique for AL measurement for our study subjects.

Ocular axial length is strongly associated with the incidence of primary angle closure. Biometric studies have shown that acute primary angle closure glaucoma is associated with shorter axial length (AL) (Foster, 2002; Lowe, 1970; Seah *et al.,* 1997; Wong *et al.,* 2000). Eyes with an axial length of less than 23 mm are at particular risk to develop primary angle

closure glaucoma (Sherpa D, *et al*, 2008). In the Bhaktapur Glaucoma Studies, eyes in the Nepalese population with occludable angle and angle-closure glaucoma appear to have significantly shallower anterior chambers and shorter axial lengths when compared with the normal group (Suman ST, *et al*, 2011). In a cohort of Chinese patients with PACG, a shorter axial length (AL) was identified as a risk factor for progressive VF defects in Chinese patients under treatment for PACG (Fan *et al.*, 2013). In a 6 years population based study involved adults aged 40 years and older from rural and urban South India, shorter AL is a strong predictor for progression of PACG (Vijaya L *et al*, 2016).

1.3.2 Anterior chamber depth and PACG

ACD is measured along posterior corneal surface to the anterior pole of the lens (Hitzenberger, 1991).

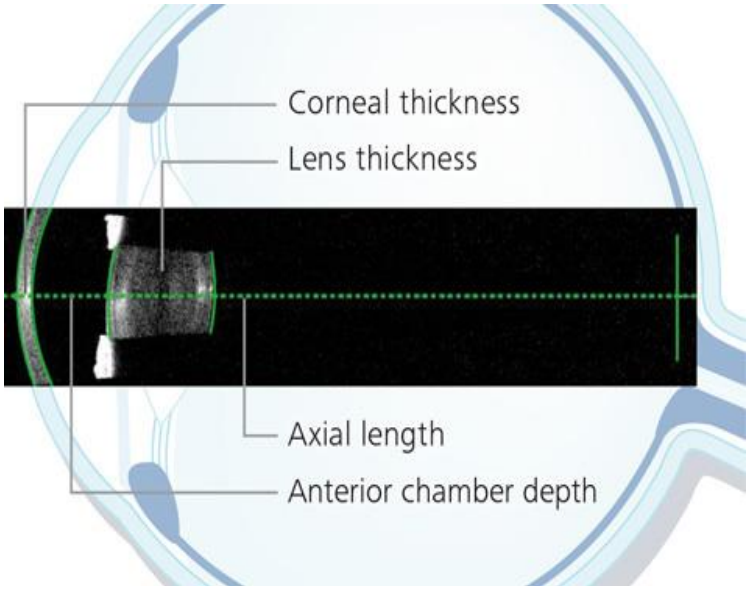


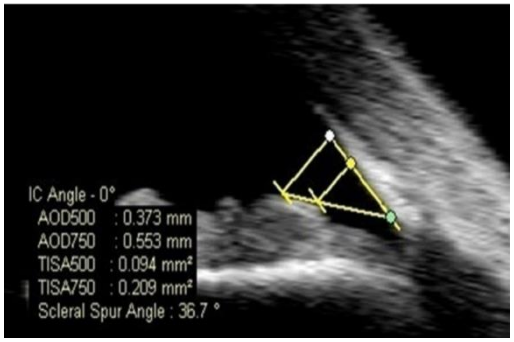
Figure 2: Illustration demonstrates ACD using IOL Master in the subject

ACD measure by IOL Master demonstrates good reliability and consistency. Hence it was the chosen method ACD measurement for our study subjects apart from measuring AL.

Numerous studies revealed that shallower anterior chamber is one of the contributing factors for primary angle closure glaucoma. The association of anterior chamber depth with primary angle closure glaucoma is evidenced by a recent study evaluating anterior chamber depth in the East Asian population (Devereux JG, *et al*, 2000*;* Aung T, *et al*, 2005). Moreover, according to an ocular biometric study published in 2013 (Chen YY, *et al*, 2013), shallower anterior chamber depth predisposes subjects with primary angle closure to progress to primary angle closure glaucoma. Lan YW et al 2007 also reported that eyes with PACG and Chronic Angle Closure Glaucoma (CACG) with or without Acute Angle Closure (AAC) had shorter AL (Lan *et al.*, 2007).

1.3.3 Anterior chamber angle(ACA) and PACG

The ACA is defined in degrees, in which the angle recess forms the apex and the two sides of the angle is formed by drawing the lines through the points defining the angle opening distance (AOD 500) (Salim S, *2012*).



According to Mohammad Pakravan, *et al,* 2012, individuals with anterior chamber angle ≤26° should have prophylactic laser peripheral iridectomy (LPI) as they are at high risk to develop primary angle closure attack, with a sensitivity of 77.3% and a specificity of 88.2% respectively. However, there is no much data to suggest such an arbitrary cutoff point for LPI.

1.4 RATIONALE OF STUDY

Risks factors for progression in glaucoma have been mostly obtained from studies on open angle glaucoma, and only scanty data available for progression in PACG. Crowded anterior segment is a known risk for developing PACG. *Wang et al* 2002 reported that Chinese eyes are anatomically predisposed to PACG. However, among the above-mentioned ocular biometrics, axial length is the only ocular biometric parameter consistently associated with progression of PACG. ACD was not associated with VF progression in both Quek et al and Fan et al's study (Fan *et al.*, 2013; Quek *et al.*, 2011). However, it is still studied in view of its close association with PACG. Up to date, there are no reports on the association of ACD with progression of PACG, and the association of various anterior segment biometry parameters with progression of PACG up to date remains unconfirmed.

The association of anterior segment biometry parameters with progression of PACG is still not well researched up to current date. Despite of the high prevalence of PACG in Chinese patients, but surprisingly Malay PACG patients tends to progress more rapidly than Chinese patients based on a retrospective study by Liza-Sharmini AT, et al (Liza-Sharmini *et al.*, 2014). Hence, this study to compare the anterior segment biometry parameters in Malay and Chinese PACG patients which will aid in understanding the role of anterior segment biometry parameters with progression of PACG. Identification of susceptible patient for progression will help in customization of treatment to prevent further glaucomatous damage.

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