PROGNOSTIC FACTORS ON TRABECULECTOMY AMONG GLAUCOMA PATIENTS IN KELANTAN

by

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LIST OF ABBREVIATIONS

IOP	Intraocular pressure
ACG	Angle closure glaucoma
CI	Confidence interval
df	Degree of freedom
HR	Hazard ratio
KM	Kaplan Meier
MC	Multicollinearity
mmHg	Millimetre mercury
OAG	Open angle glaucoma
PACG	Primary angle closure glaucoma
PH	Proportional hazard
POAG	Primary open angle glaucoma
RGC	Retinal ganglion cells
SD	Standard deviation
VIF	Variation inflation factor

LIST OF SYMBOLS

<	Less than
>	More than
=	Less than and equal to
=	More than and equal to
=	Equal to
a	Alpha
ß	Beta
%	Percentage

FAKTOR-FAKTOR PROGNOSTIK DI KALANGAN PESAKIT GLAUKOMA YANG MENJALANI PEMBEDAHAN TRABEKULEKTOMI DI KELANTAN

ABSTRAK

Pengenalan: Kajian kadar kejayaan trabekulektomi di kalangan penduduk Malaysia adalah kurang sedangkan informasi berkenaan kadar kejayaan trabekulektomi dan faktor-faktor prognostik bagi hasil pembedahan tersebut adalah amat diperlukan bagi membantu pakar oftalmologi dalam menentukan prognosis kejayaan pembedahan dan membantu meningkatkan kadar kejayaan pembedahan tersebut.

Objektif: Kajian ini bertujuan untuk menentukan kadar kejayaan selepas lima tahun pembedahan trabekulektomi dan mengenalpasti faktor-faktor prognostik yang mungkin mempengaruhi hasil trabekulektomi di kalangan pesakit glaukoma yang dirawat di HUSM.

Metodologi: Satu kajian menggunakan ulasan rekod secara retrospektif melibatkan 96 orang pesakit glaucoma (96 biji mata) yang menjalani trabekulektomi dari 1 Januari 1990 hingga 31 Julai 2006 telah dijalankan. Perkembangan susulan lengkap selama setahun selepas proses pemilihan subjek juga turut dijalankan dari 1 Ogos 2006 ke 31 Julai 2007. Maklumat yang telah dikenalpasti dan status trabekulektomi sehingga 31 Julai 2007 telah direkodkan ke dalam borang rekod klinikal dijalankan oleh penyiasat utama dengan bantuan pakar oftalmologi. Analisa statistik dibuat berdasarkan kaedah "Kaplan Meire" dan "Cox regression".

Keputusan: Masa pertengahan bagi kejayaan trabekulektomi adalah 18.8 bulan dan kadar kumulatif kejayaan trabekulektomi adalah 36.1% (95% CI: 25.6, 46.8) pada tahun kelima. Berdasarkan analisa "multivariable Cox regression" setelah mengambil kira faktor-faktor lain, didapati faktor prognostik yang signifikan secara statistik dalam mempengaruhi hasil trabekulektomi ialah sejarah lampau pembedahan mata sebelum menjalani trabekulektomi (HR=2.31, 95% CI: 1.21, 4.41; p=0.019).

Kesimpulan: Kadar kejayaan trabekulektomi di kalangan pesakit glaukoma yang dirawat di HUSM adalah rendah. Sejarah lampau pembedahan mata merupakan faktor prognostik yang signifikan, dimana risiko kegagalan trabekulektomi adalah 2.31 kali ganda.

Adalah dicadangkan supaya penjagaan selepas pembedahan trabekulektomi yang lebih baik dikalangan pesakit yang mempunyai sejarah lampau pembedahan mata bagi meningkatkan kadar kejayaan pembedahan tersebut.

ABSTRACT

Introduction: The study on trabeculectomy success rate in Malaysian population was relatively scarce. Information on trabeculectomy success rate and prognostic factors for trabeculectomy outcome is needed to help ophthalmologist to determine the prognosis and search for better way to increase success rate of trabeculectomy.

Objectives: To determine the five year trabeculectomy success rate and to identify the prognostic factors that may influence the trabeculectomy outcome among glaucoma patients treated at HUSM.

Methodology: A retrospective record review study was conducted involving 96 glaucoma patients (96 eyes) who underwent trabeculectomy from 1st January 1990 to 31st July 2006. Additional follow-up of one year after the recruitment of the study subjects was done from 1st August 2006 to 31st July 2007. All patients who fulfilled the selection criteria were included in the study. The medical records were reviewed by a single researcher with the help of senior consultant of ophthalmology and important information on the variables of interest and trabeculectomy outcome status were collected and recorded into a clinical form. The Kaplan Meier and Cox Proportional Hazards regression analysis was used in statistical analysis.

Results: The median trabeculectomy success time was 18.8 months and the overall trabeculectomy success rate was 36.1% (95% CI: 25.6, 46.8) at five year. Based on the Cox's regression analysis after adjusting other variables, the significant prognostic factors that may influence trabeculectomy outcome was history of previous ocular surgery (HR=2.31, 95% CI: 1.21, 4.41; p=0.019).

Conclusion: Trabeculectomy success rate for glaucoma patients at HUSM was acceptably low. The history of previous ocular surgery was identified as the only significant prognostic factor for trabeculectomy failure.

Better post trabeculectomy management for glaucoma patient that had undergone previous ocular surgery is recommended to obtain higher trabeculectomy success rate in those patient.

CHAPTER 1

INTRODUCTION AND LITERATURE REVIEW

1.1 Introduction

Glaucoma is defined as a progressive optic neuropathy with characteristic optic disc cupping and visual field loss (Ritch *et al.*, 1996). Glaucoma is the second leading cause of blindness world wide after cataract (Quigley and Broman, 2006). Glaucoma is also known as the thief of sight, robbing the vision silently (Ritch *et al.*, 1996).

It has many risk factors such as age, race, sex, intraocular pressure (IOP), optic nerve changes, corneal thickness, refractive error, systemic diseases, family history and trauma. However, raised IOP is the only modifiable risk factor (Gupta *et al.*, 2006).

Adult glaucoma falls into two categories based on the status of the angle structure; open angle glaucoma (OAG) and angle closure glaucoma (ACG) (Shields, 1997). Based on visual field damage assessment, glaucoma may further classified into early, moderate and advanced glaucoma (Hodapp *et al.*, 1993).

OAG was the most common form of glaucoma and it accounted for 19% of all blindness among African-Americans compared to 6% in Caucasians (Shields, 1997). It is estimated that 40 million would become blind by 2020 and half of it was in Asia. ACG is the main culprit in Asia especially among Chinese population (Quigley and Broman, 2006).

In OAG, the aqueous humour has free access to the trabecular meshwork, which is the drainage apparatus in the anterior chamber angle. However, there is impairment of aqueous humour drainage through the trabecular meshwork itself, and this result in increased IOP. Meanwhile in ACG, the root of the iris is in apposition to the trabecular meshwork, and this prevents aqueous humour leaving the eye. Compared to OAG, ACG outcome is more severe because of it sudden progression and if not treat immediately it may cause blindness (Shields, 1997).

In glaucoma, the eye's drainage system becomes clogged so the intraocular fluid cannot drain (Shields, 1997). As the fluid builds up, it causes pressure to build within the eye. High pressure damages the sensitive retinal ganglion cells and results in vision loss (Shields, 1997). The vision loss in glaucoma is due to death of retinal ganglion cells, which is thought to occur by a mechanism of genetically programmed cell death apoptosis (Kerrigan *et al.*, 1997).

Currently, IOP is the only modifiable risk factor and lowering IOP proven to be beneficial in reducing the risk of progression of visual field loss in glaucoma (Heijl *et al.*, 2002). The reduction of IOP is achievable by medical treatment, laser or surgical intervention. Trabeculectomy, which is performed by creating a fistula to improve the aqueous outflow and reduced the IOP was introduced by Sugar (Sugar, 1961) and improved by Cairns (Cairns, 1969), is the preferred procedure for the surgical management for various types of glaucoma.

After more than 30 years since the introduction of trabeculectomy, it still remains the most commonly used effective incisional surgery for glaucoma (Lichter *et al.*, 2001).

Based on various studies that compared the initial trabeculectomy with medical treatment, found that trabeculectomy provides consistently lower IOP than medical therapy (Jay and Murray, 1988; Migdal *et al.*, 1994; Burr *et al.*, 2004). The long-term success of trabeculectomy based on IOP control varies from 55% to 98%, depending on follow-up time and the criteria used to define successful cases (Jacobi *et al.*, 1999).

Various risk factors had been identified to be associated with trabeculectomy failure including the type of glaucoma (Allen *et al.*, 1982), ethnicity (Miller and Barber, 1981), previous ocular surgery (Inaba, 1982) and previous topical antiglaucoma medication (Broadway *et al.*, 1994b).

Survival analysis is a collection of statistical procedures for data analysis in which the outcome variable of interest is "time until an event occurs". In survival analysis, the time variable usually referred to survival time. Survival time is the time that an individual has "survived" over some follow-up period. The event in survival analysis typically refers as a failure since the event of interest is death, disease incidence or some other negative individual experience (Klembaum and Klein, 2005). Most of studies use some or all of Kaplan-Meier (KM) plots, log-rank tests and Cox proportional hazards regression in answering questions about patients' survival (Clark *et al.*, 2003; Klembaum and Klein, 2005).

Races seem to play an important factor. Blacks were believed to have poorer success rate (Miller and Barber, 1981) compared to Caucasians (Diestelhorst *et al.*, 1999) and Asians (Wong *et al.*, 1998). The aim of this study was to evaluate the trabeculectomy success rate and contributing prognostic factors that influences the trabeculectomy outcome in terms of IOP among Kelantanese.

1.2 Overview of the eye structure

The outer layer of the eyeball is called the sclera. The sclera is a thin, tough, leathery protective shell which is the white of the eye. The front portion of the shell is called the cornea. The cornea is a clear tissue through which light rays enter the eye. The coloured portion of the eye is called the iris. The iris contains muscles which control the size of the pupil, regulating the amount of light allowed to enter the eye (Shields, 1997; Galloway *et al.*, 2006) (Figure 1.1).

The pupil, which is the dark-coloured area in the centre of the iris, opens and closes depending upon how much light is present. The lens, which is behind the iris, adjusts its shape and thickness to focus the image onto the retina. The retina then delivers the image to the brain via nerve signals which are sent through the optic nerve to the brain, which processes these signals into visual image (Shields, 1997; Galloway *et al.*, 2006).

The interior of the eye is filled with fluid. A gel-like substance called vitreous fills the centre region of the eye. This region is called the vitreous cavity. The anterior chamber, or front compartment of the eye, is bounded by the cornea, iris, pupil, and lens. It is filled with a watery fluid called the aqueous humour. This fluid nourishes the cornea and the lens, providing them with oxygen and vital nutrients. The aqueous humour also provides the necessary pressure to help maintain the shape of the eye. This pressure is known as the IOP (Shields, 1997; Galloway *et al.*, 2006).

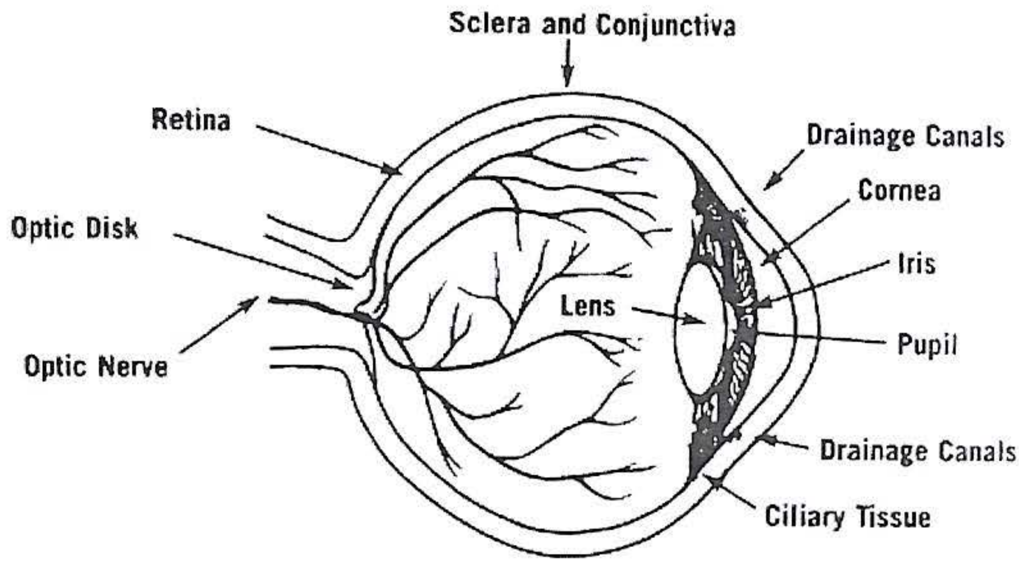

Figure 1.1 Anatomy of the eye, (Robin Parks, 2006).

Aqueous humour is continuously produced by ciliary body and circulated through the anterior chamber before draining out of the eye. This continuous flow of fluid nourishes the lens and the cornea and also removes unwanted debris. A healthy eye produces aqueous humour at the same rate that it drains fluid, thus maintaining a normal pressure (Shields, 1997; Galloway *et al.*, 2006).

Aqueous humour exits the eye through a drainage system located at the angle formed where the iris and the cornea meet. Here it passes through a sieve-like system of spongy tissue called the trabecular meshwork and drains into a channel called Schlemm's canal. The fluid then merges into bloodstream (Shields, 1997; Galloway *et al.*, 2006).

When the drainage system fail to function properly especially when trabecular meshwork is clogged, the aqueous humour unable to be filtered out of the eye at its normal rate and pressure builds within the eye which resulted in increase of the eye pressure and often associated with gradual damage to the nerve fibres that make up the optic nerve. Being recently mentioned situation sometimes lead to visual loss. This pathologic condition is known as glaucoma (Shields, 1997).

1.3 Glaucoma

Historically, this group of condition had been studied and recognized by the Greek as early 400 BC. Hippocrates described the condition as glaucosis, the bluish-green hue that affects the eye. But the same term was also applied to a larger group of blinding condition including cataract. Old Arabic writing also explained the association between IOP with this kind of eye disorder. Despite those findings, our modern understanding of glaucoma dates only back to the mid-19^{th} century, which recognizes the glaucoma as a distinct group of ocular disorder (Shields, 1997).

Retinal ganglion cells (RGC), particularly the optic nerve fibre or axon are the primary site for glaucomatous injury. Among clinical sign of glaucoma include thinning of neuroretinal rim and excavation of the optic nerve head (Weinreb, 2007). IOP was initially known as causative factor but recently is known as the only modifiable risk factor (Gupta, 2006). Age is actually the most important risk factor (Weinreb, 2004).

Measurement of the IOP in a large number of normal patients reveals a normal distribution extending from pressures of 10–12 mmHg to 25–28 mmHg. The pattern of distribution fits a Gaussian curve, so that the majority of patients have a pressure of about 16 mmHg. For clinical purposes, it is necessary to set an arbitrary upper limit of normal. The eye can stand low pressures remarkably well, but when the pressure is abnormally high, the circulation of blood through the eye becomes jeopardized and serious damage can ensue. For clinical purposes, an upper level of 21 mmHg is often accepted. Above this level, suspicions are raised and further investigations should be made (Galloway *et al.*, 2006).

The gold-standard method of IOP measurement is Goldmann applanation tonometry where a prism is used to apply a force to the cornea to indent and flatten its surface (Goldmann, 1955). The Goldmann tonometer is supplied as an accessory to the slit-lamp microscope (Galloway *et al.*, 2006).

1.4 Epidemiology of glaucoma

Glaucoma is the second leading cause of blindness world wide after cataract (Resnikoff *et al.*, 2004). A data from United States of America in 1990s, had estimated that the total number of glaucoma cases among those 40 years of age or older to be approximately 1.5 million among Caucasians and others (including Hispanics, Asians and Native Americans) and 0.5 million among African Americans (Thylefors, 1995).

In Europe, glaucoma accounts for 7% to 15% of all blind registrations and is second to age related macular degeneration as the main cause (Fuchs *et al.*, 1992). OAG is the most common form of glaucoma in Europe. It accounts for 75% to 95% of primary glaucoma except in people of Eastern Asians (Mongoloid) descent, where ACG is more prevalence (Congdon *et al.*, 1992).

Previous studies in Western populations show significant racial or ethnic variation between Whites and Blacks, largely related to variation in the prevalence of OAG (Friedman, 2004). In the Baltimore Eye Survey, the prevalence of OAG was about four times higher in Blacks compared to White (Tielsch *et al.*, 1991).

It has been estimated that half of the world's 70 million people with glaucoma reside in Asia (Quigley, 1996), and that in China alone, nearly 10 million people have glaucoma (Foster *et al.*, 2003). In the recent years, several studies on the epidemiology of glaucoma in Asian people were conducted (Shiose *et al.*, 1991; Dandona *et al.*, 2000). The prevalence of glaucoma range from 2.1% in Bangladesh to 5.0% in Japanese population.

Although it has been hypothesised that ACG is the most common type of glaucoma in Chinese people (Congdon *et al.*, 2002), however population based study indicates that OAG is more common than ACG (Foster *et al.*, 2000). Tanjong Pagar Survey which was conducted in Singapore found, 50% had OAG and only 30% had ACG (Foster *et al.*, 2000), further emphasize that ACG is common in Asians as compared to Caucasian but OAG is still the main type of glaucoma.

In Malaysia a national survey was conducted among children attending six schools for the blind to determine the causes of blindness and severe visual impairment. Glaucoma was identified for 7.2% as causes of blindness and 3.6% for severe visual impairment (Reddy and Tan, 2002).

1.5 Treatment of glaucoma

Treatment of glaucoma aims to prevent visual disability and preserve overall well being for patients with glaucoma. IOP is the only risk factor that can be treated nowadays. IOP lowering can be achieved by using medical treatment, laser and surgical intervention (Burr *et al.*, 2004).

Medical treatment can be delivered topically as eye drops or systemically. For more that two decades the first line of medical treatment for OAG glaucoma has been topical beta-blockers, which provide good IOP lowering effect but with the possibility of adverse side effects, particularly in elderly population (Diggory *et al.*, 1995). In the mid 1990s alternative medical treatments such as topical carbonic anhydrase inhibitors, alpha2-agonist and recently prostaglandin analogous were introduced with better option plus pressure lowering effect but with higher cost. This mode of treatment requires great compliance from the patients (Bateman *et al.*, 2002).

Glaucoma drainage surgery aims to lower the IOP by creating an alternative route for aqueous humour outflow, which have evolved over 30 to 40 years from full thickness procedures, to guarded filtration procedures. Full thickness procedures are now not recommended due to higher risk of complications compared to guarded filtration procedures. Example of surgical interventions includes trabeculectomy (Watson and Grierson, 1980), non-penetrating trabeculectomy (Netland, 2001) and glaucoma drainage devices (Lim *et al.*, 1998).

1.6 Trabeculectomy

Trabeculectomy is a guarded filtration procedure whereby the IOP is lowered by creation of a fistula to drain aqueous humour from within the eye globe into sub-conjuctival space by creating a filtering bleb (Burr *et al.*, 2004). This procedure created small channel between the anterior chamber and subconjunctival, allowing aqueous to drain into subconjunctival region by passing the trabecular meshwork (Sugar, 1961).

For the past 30 years, surgical trabeculectomy that was first introduced by Sugar in 1961 on animals (Sugar, 1961) had been the filtering procedure of choice for managing glaucoma. Despite of being introduced by Sugar in 1961 on laboratory animals, only after 1969 this method had been popular after Cairns applied it in clinical setting by modifying the technique (Cairns, 1969). After the implementation of this surgical technique several surgical improvement had been made to enhance the success rate of the procedure, which include the used of antimetabolites to increase success rate (Palmer, 1991), laser suture lysis (Hoskins and Migliazzo, 1984) and releasable suture to increase bleb survival (McAllister and Wilson, 1986).

There are many previous studies that compared trabeculectomy and medical therapy (Bateman *et al.*, 2002; Burr *et al.*, 2004) which concluded that trabeculectomy provide more consistent IOP lowering effect than medical therapy (Migdal *et al.*, 1994; Lichter *et al.*, 2001). More stable IOP is achieved by reducing the mean diurnal IOP fluctuation, the range of diurnal variation and the day-to-day variability. Unstable IOP fluctuation is known to be related to glaucoma progression (Wilensky *et al.*, 1994). Another advantages of trabeculectomy is cheaper treatment without the need of expensive antiglaucoma medication in a long run and compliance is not questionable anymore (Schwartz and Budenz, 2004).

However it is an invasive procedure and exposed patient to other risk such as intraoperative and postoperative complication (Shields, 1997). The intraoperative complications include button hole, bleeding and expulsion haemorrhage. Infection, hypotony, hypertony and choroidal detachment are among devastating postoperative complication (Shields, 1997). The success rate of trabeculectomy is not over a long period since it is susceptible to failure in IOP lowering effect especially due to bleb failure (Schwartz and Budenz, 2004).

1.7 Trabeculectomy outcome

Raised intraocular pressure is a major risk factor for the development of glaucoma. It was previously thought that raised IOP was part of the disease definition but epidemiological studies that revealed the presence of glaucoma without raised IOP, and raised IOP without glaucoma, led to re-evaluation of the relationship between the two. However, majority of interventions for glaucoma are aimed at reduction of IOP (Hatt *et al.*, 2006).

Since the first trabeculectomy by Cairns 1968, there were no standardized criteria to define success of trabeculectomy outcome. The exact definition of success varies across various studies. The cut of point or the level of IOP varies from 22 mmHg to 18 mmHg (Rolim deMoura *et al.*, 2007). A 20% decrease from initial IOP was also used as primary outcome (Damji *et al.*, 2006). Some studies even considered the need for another filtering surgery as their failure criteria (Watson *et al.*, 1984; Grayson *et al.*, 1993). Later, the success was further defined whether it was controlled without or with postoperative antiglaucoma medication, which then divided into complete and qualified success. Complete success generally was defined as IOP reduction of 22 – 18 mmHg without the need of postoperative medication, an additional of one medication is considered as qualified success (Mietz *et al.*, 1999).

A retrospective study done in Cologne, Germany defined success as IOP <21 mmHg throughout the entire study period (Diestelhorst *et al.*, 1999). In another study done in Birmingham, UK successful IOP was defined as unqualified where IOP was less than or equal 18 mmHg without medication and qualified where anti glaucomatous therapy was required to maintain the IOP at 18 mmHg (Kyprianou *et al.*, 2007).

This lack of standardization creates a lot of difficulties in meta-analysis or systemic review in providing general guidelines to ophthalmologist. One successful surgery could be a failure in another part of the world.

1.8 Trabeculectomy success rate

The long-term success in term of IOP reduction post trabeculectomy ranged from 40% to 98%, depending on follow-up time, type of glaucoma, variables of interest, type of population and the criteria used to define successful outcome (Mahdavi *et al.*, 1995; Shin *et al.*, 1996; Sharif and Selvarajah, 1997; Lachkar *et al.*, 1997; Wong *et al.*, 1998; Beatty *et al.*, 1998; Molteno *et al.*, 1999; Diestelhorst *et al.*, 1999; Erhnooth *et al.*, 2002; Hooi and Hooi, 2003; Mietz and Krieglstein, 2006; Fukuchi *et al.*, 2006; Kyprianou *et al.*, 2007; Law *et al.*, 2007). In most studies, complete success in terms of IOP was described as an IOP of 21 mmHg or less, without medication (Table 1.1).

Most of the study on Whites showed better trabeculectomy success rate in term of IOP control when compared to Asian. For example, an overall success rate in term of IOP control was higher in Helsinki, Finland (Erhnooth *et al.*, 2002) compared to studies done in Malaysia (Sharif and Selvarajah, 1997; Hooi and Hooi, 2003). In those studies, the overall cumulative success rates for Finish at year two was claimed at 70% compared to only 46.9% and 51% respectively in the studies done in Johor Baharu and Kuala Lumpur. However a study done in Cologne, Germany (Diestelhorst *et al.*, 1999) showed comparable result when compared with the study done in Johore Baharu (Hooi and Hooi, 2003). The two-year overall cumulative success rate was reported 53.4% in Cologne. Although overall success rate reported in Singapore (Wong *et al.*, 1998) was better than studies done in Malaysia, however the rate of overall trabeculectomy success still lower when compared to the studies done on white. Anyhow, a study done in India (Sihota *et al.*, 2004) showed better results than the study in Malaysia (Sharif and Selvarajah, 1997; Hooi and Hooi, 2003) and the results was comparable with other studies done in Europe (Lachkar *et al.*, 1997; Molteno *et al.*, 1999).

Table 1.1 Previous researches for trabeculectomy success rates

Study	Sample	Criteria of tonometric success	Overall cumulative success rate by year (%)
Birmingham (UK) (Kyprianou *et al.*, 2007)	25 patients (30 eyes)	**Unqualified success**: IOP = 18 mmHg **Qualified success**: IOP = 18 mmHg with antiglaucoma medication	**5** / **10 years** 60 / 15 %
Los Angeles (USA) (Law *et al.*, 2007)	58 patients	IOP < 22 mmHg	**1** / **3** / **4 years** 79.4 / 65.8 / 61.6 %
Niigata (Japan) (Fukuchi *et al.*, 2006)	82 patients	IOP = 22 mmHg	**1** / **2 years** 93 / 87.6 %
Cologne (Germany) (Mietz and Krieglstein, 2006)	52 patients	**Complete success:** IOP = 22 mmHg without medication **Qualified success:** IOP = 22 mmHg with medication	**1** / **2 years** 80.7 / 76.9 %
New Delhi (India) (Sihota *et al.*, 2004)	64 eyes (64 patients)	IOP = 21 mmHg with or without antiglaucoma medication	**5** / **10 years** 94 / 88 %
Johor Bahru (Malaysia) (Hooi and Hooi, 2003)	102 eyes	**Complete success** IOP < 21 mmHg without medication **Qualified Success** IOP < 21 mmHg with medication	**2** / **3 years** 46.9 / 37.7 %
Helsinki (Finland) (Erhnooth *et al.*, 2002)	138 patients (138 eyes)	**Complete success:** IOP = 21 mmHg without medication **Qualified success:** IOP = 21 mmHg with a single medication	**1** / **2** / **3** / **4 years** 82 / 70 / 64 / 52 %
Otago (New Zealand) (Molteno *et al.*, 1999)	193 patients (289 eyes)	**Cure:** IOP = 21 mmHg **Medical control:** IOP = 21 mmHg on hypotensive medication	**1** / **2** / **3** / **4** / **5 years** 98 / 97 / 96 / 95 / 95 %
Cologne (Germany) (Diestelhorst *et al.*, 1999)	547 patients	**Qualified success:** IOP < 21 mmHg	**1** / **2** / **3** / **5** / **6 years** 61 / 53.4 / 50 / 37.8 / 37.6 %
National University Hospital (Singapore) (Wong *et al.*, 1998)	89 patients	IOP < 22 mmHg without any anti glaucoma medication or surgery	**1** / **3 years** 65.1 / 51.5 %

Table 1.1 Continued

Study	Sample	Criteria of tonometric success	Overall cumulative success rate by year (%)
Birmingham UK (Beatty *et al.*, 1998)	69 patients	**Unqualified success:** IOP = 21 mmHg without antiglaucoma medication **Qualified success:** IOP = 21 mmHg with antiglaucoma medication	**1** **2** **years** 75 67 %
London (UK) (Lachkar *et al.*, 1997)	18 patients	IOP = 21 mmHg	**1** **2** **3** **4** **5 years** 98 97 82 80 78 %
Kuala Lumpur (Malaysia) (Sharif and Selvarajah, 1997)	61 eyes	IOP < 20 mmHg	**2** **years** 51 %
Detroit (USA) (Shin *et al.*, 1996) New Haven,	174 patients (174 eyes)	**Criterion I:** IOP < 20 mmHg without the need of antiglaucoma medication **Criterion II** IOP < 20 mmHg and one antiglaucoma medication	**1** **5** **years** 97 78 %
Connecticut (USA) (Mahdavi *et al.*, 1995)	78 patients	Minimum IOP reduction of 20% and IOP pressure = 20 mmHg	**3** **5** **years** 48% 40%

1.9 Prognostic factors of trabeculectomy outcome

Several prognostic factors of trabeculectomy outcome were proposed. Known factors for filtration failure after trabeculectomy include previous ocular surgery, secondary glaucoma, black race, long-term therapy with multiple topical antiglaucoma drugs and young age (Broadway and Chang, 2001; Wong *et al.*, 2006).

By definition, an eye that has previously undergone failed filtration surgery is at risk for further failure after repeated filtration because the same risk for further failure will still be present (Broadway and Chang, 2001). Factors proposed to explain this include breakdown of the blood-aqueous barrier and anatomic disturbance within the eye resulting the release of factors that stimulate wound healing (Broadway *et al.*, 1998). Previous conjuctival surgery also has been identified as a significant risk factor for failure of trabeculectomy in children (Miller and Rice, 1991).

It is generally accepted that in certain Black racial group the results of trabeculectomy are not as successful in comparison with the results in White population (Zaidi, 1980; Miller and Barber, 1981; Shin *et al.*, 1996). However the published evidence for racial differences is not strong (Broadway *et al.*, 1994a). A main reason thought for this is the great genetic heterogeneity within those of the black race (Broadway and Murdoch, 1995). So that it is important to distinguish between population of Afro-Carribean, African-European and African-American patients when assessing the surgical outcome in studies of black patients (Broadway and Chang, 2001).

Youth has been considered a significant risk factor for failure of trabeculectomy for many years (Beauchamp and Parks, 1979). Previous results also showed that children younger than age 7 gave poor trabeculectomy survival outcome (Miller and Rice, 1991).

The results of trabeculectomy in eyes with certain type of glaucoma are poor. Secondary glaucoma was thought to have poorer trabeculectomy survival outcome. Unaugmented trabeculectomy in eyes with neovascular glaucoma is highly likely to fail (Mill, 1981). Traumatic glaucoma is most commonly caused by blunt contusion, but can also occur by many reasons after penetrating ocular surgery. The results of filtration surgery are also considered relatively poor in eyes that have sustained trauma (Broadway and Chang, 2001). Uveitic glaucoma also generally gives poorer trabeculectomy survival outcome (Towler *et al.*, 1995).

Long term combination medical therapy has been shown to induce subclinical inflammation with increase in the number of fibroblasts, lymphocytes, macrophage and mast cells (Sherwood *et al.*, 1989). Those cells were associated with a significantly lower trabeculectomy success rate in comparison with patients undergoing initial trabeculectomy (Broadway *et al.*, 1994b).

Patients diagnosed with diabetes mellitus also was found significantly associated with trabeculectomy failure. In a study done at Detroit, America has reported patients that have diabetes mellitus during surgery will have a lower trabeculectomy survival outcome. In that study, black race, preoperative > 20 mmHg, preoperative medication more than two were also found significance prognostic factors in trabeculectomy failure (Shin *et al.*, 1996).

1.10 Survival Analysis

In most of cancer studies, the main goal interested was the time to an event of interest. The other name for the time was survival time. However, this term can also be referred or applied to the time survived from complete remission to relapse or progression as equally as to the time from diagnosis to death (Clark *et al.*, 2003). In the context of this study, this term was applied to determine trabeculectomy success rate from the first day of operation till the last date of filtration failure based on several defined criteria.

If the event of interest occurred in all individuals, many statistical methods could be applicable for analysis. However, in many studies, especially in biomedical and epidemiology studies it was common that at the end of follow up some of the subjects or individuals do not experience the event of interest. In addition, survival data were rarely normally distributed. They were usually skewed in nature and comprise commonly of many early events and relatively few late ones. Hence, it was these features of the data that made the special methods called survival analysis essential (Clark *et al.*, 2003).

All of those special features could be made sensible because in survival analysis all others subjects or individuals who did not experience the event of interest need to be treated as censored observations in statistical analysis. The recognition of censored observations is crucial. Survival time would be underestimated if they were not treated as "censored" in an analysis. Censored observations are patients who have still not experienced the event of interest when the study is closed, those who were lost to follow-up and those whose deaths were unrelated (Clark *et al.*, 2003).

The (Kaplan-Meier) KM survival curve, a plot of the KM survival probability against time, provides a useful summary of the data that can be used to estimate measures such as median survival time. Median survival time was used rather than mean survival time because in the distribution of most survival data, most of it had largely skewed (Clark *et al.*, 2003).

In multivariate approach of survival analysis data, the Cox proportional hazard regression model (PH) (Cox, 1972) is the commonly used analysis for analyzing survival time data in medical research. The relationship between the event incidence, as expressed by the hazard function and a set of covariates can be determined. Another feature that makes the Cox PH model is interesting from another model is that the baseline hazard function is estimated nonparametrically, so the survival time is not assumed to follow a particular statistical distribution like most other statistical models (Bradburn *et al.*, 2003).

The Cox model was essentially a multiple linear regression of the hazard on the variable x_i , with the baseline hazard being an intercept term that varies with time. The covariates then act multiplicatively on the hazard at any point in time, and this provides us with the assumption of PH model: the hazard of event in any group was a constant multiple of hazards in any other. This assumption implies that the hazards curves for the groups should be proportional and cannot cross each other (Bradburn *et al.*, 2003).

Proportional implies that the quantities exponent (b_i) was called hazards ratio. A value of b_i greater than zero, or equivalently a hazard ratio greater than one, indicates that as the value of the *i*th covariates increases, the event hazard increases and thus the length of survival decreases. In a simpler way, a hazard ratio above one indicates a covariate that was positively associated in the event probability, and thus is negatively associated with the length of survival. This proportionality assumption is often appropriate for survival time data but it was important to verify that it holds. In this model hazard are proportional whereas hazard ratios are constant across time (Bradburn *et al.*, 2003).

1.11 Justification of study

In Malaysia, data of success rate of Malaysians' glaucoma patients that had undergone trabeculectomy are relatively scarce. The differences in demography, races may give different results in trabeculectomy success rate. Identifying the prognostic factors will help ophthalmologists to improve the trabeculectomy success rate among glaucoma patients in our local practice.

1.12 Conceptual framework

Figure 1.2 shows the conceptual framework of the present study. Glaucoma patients treated with trabeculectomy at HUSM were selected and then checked for inclusion and exclusion criteria. Type of glaucoma, race, number of preoperative medication, IOP before surgery were some of the predictor for trabeculectomy outcome were then taken from patient's folder. After trabeculectomy, the patient was given follow-up. All of the patients in this study had been under follow-up until they experienced the defined failure criteria till the end of study period. There were also patients who died which were not related with trabeculectomy, patients who not experienced defined failure criteria (trabeculectomy was success) and patients who lost of follow up.

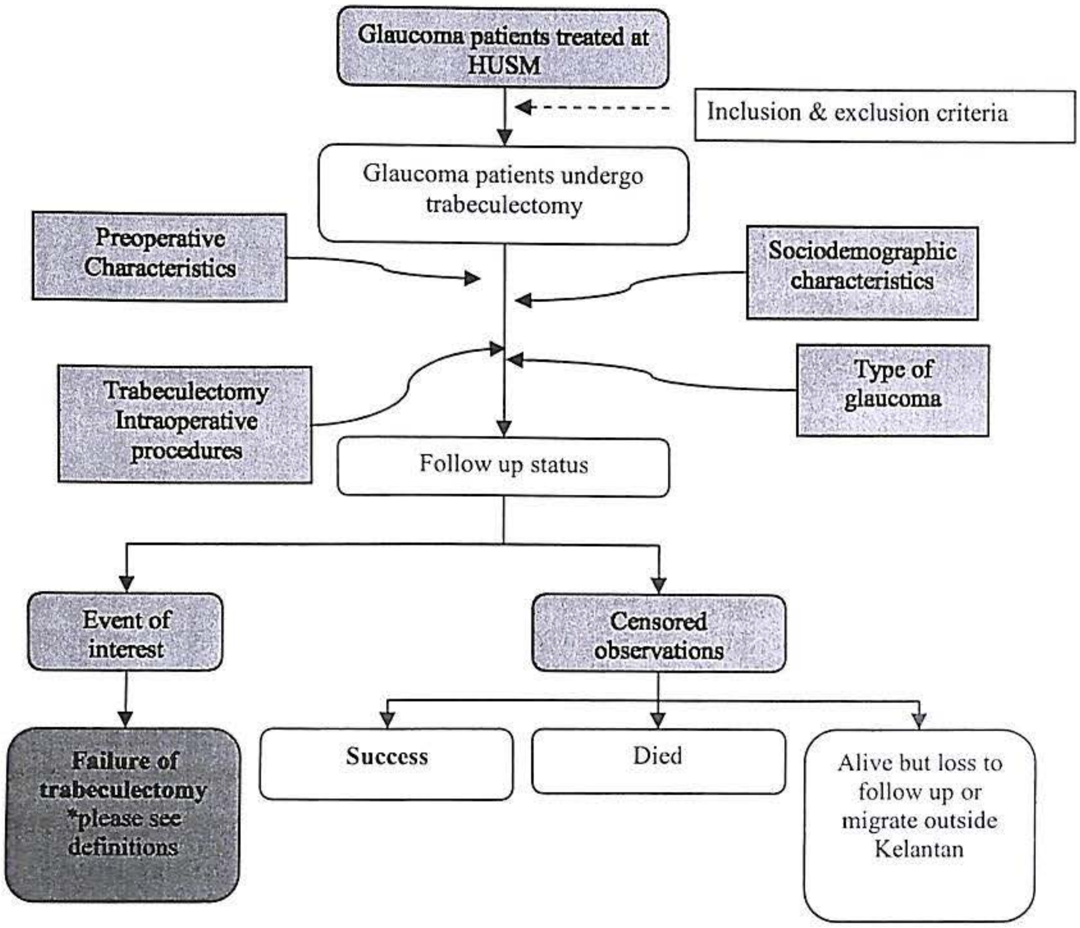

Figure 1.2 Conceptual framework of the present study

CHAPTER 2

OBJECTIVE OF STUDY

2.1 General objectives

To determine the trabeculectomy success rate in terms of intraocular pressure (IOP) and to identify prognostic factors that influence trabeculectomy outcome in various types of glaucoma in Kelantan.

2.2 Specific objectives

1. To determine the five-year success rate after trabeculectomy.

2. To identify the prognostic factors that influences the trabeculectomy outcome among glaucoma patients.

2.3 Research questions

1. What is the five-year success rate after trabeculectomy?

2. What are the prognostic factors that influence the trabeculectomy outcome among glaucoma patients?