PROGNOSTIC FACTORS OF VISION LOSS AFTER VITRECTOMY SURGERY AMONG PATIENTS WITH PROLIFERATIVE DIABETIC RETINOPATHY IN HOSPITAL RAJA PEREMPUAN ZAINAB II

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by

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LIST OF ABBREVIATIONS

ADED	Advanced Diabetic Eye Disease
CI	Confidence Interval
CHD	Coronary Heart Disease
CKD	Chronic Kidney Disease
CVA	Cerebrovascular Accident
Df	Degree of Freedom
DR	Diabetic Retinopathy
DM	Diabetes Mellitus
ERM	Epiretinal Membrane
HPT	Hypertension
HR	Hazard Ratio
HRPZ II	Hospital Raja Perempuan Zainab II
IHD	Ischemic Heart Disease
JEPeM	Jabatan Etika Penyelidikan Manusia
LDLC	Low Density Lipoprotein Cholesterol
LogMar	Log of Minimum Angle of Resolution
MREC	Medical Research and Ethics Committee

NMRR	National Medical Research Registry
NPDR	Non-Proliferative Diabetic Retinopathy
NVI	Neovascularization of Iris
NVG	Neovascular Glaucoma
PDR	Proliferative Diabetic Retinopathy
PPV	Pars Plana Vitrectomy
PS	Power and Sample size software
RRD	Rhegmategenous Retinal Detachment
SD	Standard Deviation
SPSS	Statistical Package for the Social Sciences
TRD	Tractional Retinal Detachment
VA	Visual Acuity
VH	Vitreous Hemorrhage
VIF	Variation Inflation Factor

LIST OF SYMBOLS

α	Level of significance/ Type I error
1-β	Power
β	Standardized coefficients/ Type II error
>	Less than
<	More than
≥	More than or equal to
≤	Less than or equal to
±	Plus or minus
%	Percentage
b	Regression coefficient
P	P-value
n	Number of experimental patients / sample size
m	Ratio of control to experimental
m1	Median survival time on control treatment
A	Accrual time during which patients are recruited
F	Additional follow-up time after end of recruitment

FAKTOR - FAKTOR PROGNOSTIK KEHILANGAN PENGLIHATAN SELEPAS PEMBEDAHAN VITREKTOMI DALAM KALANGAN PESAKIT DIABETIK RETINOPATI PROLIFERATIF DI HOSPITAL RAJA PEREMPUAN ZAINAB II

ABSTRAK

Latar belakang kajian: Diabetik Retinopati Proliferatif (DRP) adalah salah satu penyebab utama buta di seluruh dunia. Perkembangannya berkait rapat dengan progresif retina iskemia daripada diabetik retinopati manakala komplikasinya boleh membawa kepada kehilangan penglihatan, saraf retina lekang, dan pendarahan vitreous. Vitrektomi adalah asas rawatan apabila komplikasi DRP yang megancam penglihatan mata seperti pendarahan vitreous dan saraf retina lekang terjadi. Kajian ini dijalankan bertujuan untuk mengenal pasti faktor – faktor prognostik kehilangan penglihatan selepas pembedahan vitrektomi dalam kalangan pesakit DRP. **Metod:** Satu kajian kohot retrospektif, melibatkan 164 pesakit DRP yang menjalani pembedahan vitrektomi dari 1 Januari 2012 hingga 31 Disember 2016 dan mengikuti rawatan susulan di Klinik Oftalmologi Hospital Raja Perempuan Zainab II. Nilai ketajaman penglihatan ditentukan dengan mengenal pasti garis yang boleh dibaca oleh pesakit berdasarkan carta Snellen. Sudut resolusi minimum dan nilai log (LogMar) diperoleh dengan membahagi penyebut dan pengangka daripada nilai ketajaman Snellen. Subjek dianggap mengalami kehilangan penglihatan apabila nilai ketajaman penglihatan menurun sebanyak 0.3 LogMar selepas pembedahan vitrektomi.

Kaplan Meier digunakan untuk menentukan masa median kehilangan penglihatan dan Regresi Cox Berkadar Bahaya digunakan untuk mengenal pasti faktor - faktor prognostik kehilangan penglihatan. Analisa statistik dibuat menggunakan STATA 14. **Dapatan kajian:** Purata umur pesakit adalah 52.68 tahun (Sisihan Piawai (SP) = 10.32). Pesakit terdiri daripada 47.6% lelaki dan 52.4% perempuan. Masa median keseluruhan atau median kebarangkalian kehilangan penglihatan yang diperoleh untuk kajian ini adalah 14.63 bulan (95% Selang Keyakinan (SK): 11.51, 17.75). Pesakit dengan keadaan pra-morbid penyakit jantung iskemia (PJI) (Nisbah bahaya terlaras (NB): 1.71, 95% SK: 1.06, 2.78) dan saraf retina lekang (SRL) pasca pembedahan (NB terlaras: 1.80, 95% SK: 1.16, 2.79) mempunyai risiko yang lebih tinggi untuk mendapat kehilangan penglihatan pasca vitrektomi selepas diselaraskan dengan faktor lain. **Kesimpulan:** Masa untuk kehilangan penglihatan dipengaruhi oleh keadaan pra-morbid PJI dan komplikasi SRL pasca pembedahan. Masa median atau durasi survival kehilangan penglihatan adalah lebih kurang 14 bulan secara amnya dan ini disarankan agar pesakit perlu dipantau dengan rapi sekurang-kurangnya dalam tempoh ini terutamanya kepada pesakit yang mempunyai risiko PJI.

Kata kunci: diabetik retinopati proliferatif, kehilangan penglihatan, vitrektomi, PJI, SRL pasca pembedahan

PROGNOSTIC FACTORS OF VISION LOSS AFTER VITRECTOMY SURGERY AMONG PATIENTS WITH PROLIFERATIVE DIABETIC RETINOPATHY (PDR) IN HOSPITAL RAJA PEREMPUAN ZAINAB II

ABSTRACT

Background: Proliferative diabetic retinopathy (PDR) is one of the major cause of blindness throughout the world. Its development is primarily related to progressive retinal ischemia from diabetic retinopathy while its complications could lead to vision loss, tractional retinal detachment, and vitreous hemorrhage. Vitrectomy is the mainstay of treatment when sight threatening complications of PDR such as vitreous hemorrhage and tractional detachment develop. The aim of this study was to identify the prognostic factors of vision loss after vitrectomy surgery among PDR patients. **Methods:** A retrospective cohort study involving 164 patients diagnosed with PDR that underwent vitrectomy surgery from 1st January 2012 to 31st December 2016 and were followed up at Ophthalmology Clinic Hospital Raja Perempuan Zainab II. Visual acuity values were determined by the line that the patients can recognize based on a Snellen chart. The Minimum Angle of Resolution and subsequently its log value (LogMar) was obtained by dividing the denominator by numerator of the Snellen acuity value. Subjects were considered to have vision loss when the visual acuity post vitrectomy surgery dropped by 0.3 LogMar. Kaplan Meier was used to determine the median time to vision loss and Cox Proportional Hazard regression was used to identify the prognostic factors of vision.

Statistical analysis was done using STATA 14. **Results:** The mean age of patients was 52.68 years (SD=10.32). The patients consisted of 47.6% male and 52.4% female. The overall median time or median probability of vision loss obtained for this study was 14.63 months (95% CI:11.51, 17.75). Patients with premorbid condition Ischemic Heart Disease (IHD) (Adjusted HR: 1.71, 95% CI: 1.06, 2.78) and post-operative Tractional Retinal Detachment (TRD) (Adjusted HR: 1.80, 95% CI: 1.16, 2.79) had a higher risk in having vision loss post vitrectomy after adjusting for other factors. **Conclusion:** Time to vision loss was influenced by premorbid condition of IHD and a complication of post-operative TRD. Median time or survival duration of vision loss was about 14 months in general and this suggest that patients should be followed up closely for at least this period of time, especially those with risk factors like IHD.

Keywords: proliferative diabetic retinopathy, vision loss, vitrectomy, IHD, post-operative TRD

CHAPTER 1

INTRODUCTION

1.1 Background of the study

According to the World Health Organization (WHO, 2016), the prevalence of diabetes has been rising worldwide, with an increase of almost two-fold over the last two decades. The rising trend of diabetes is due to many factors including population growth, aging, urbanization and the increasing prevalence of obesity and physical inactivity (Wild *et al*., 2004). As the prevalence of diabetes increases, the magnitude of disability secondary to diabetic eye disease-related complications likewise will increase (Faudzi *et al*., 2004). While in Malaysia, the prevalence of DR has been estimated to be 39.3% (Abougalambou and Abougalambou, 2015).

DR is the most common microvascular complication of diabetes (Mohamed *et al*., 2007). DR will affect nearly all diabetic patients, proportional to the duration of the disease, although controlling the blood pressure and blood sugar may delay its onset and the progression (Hendrick *et al.,* 2015). After two decades of disease, almost all Type 1 diabetic patients will have some degree of retinopathy with more than 80 % insulin-treated for Type 2 diabetic patients and 50 % of those not requiring insulin (Romero-Aroca *et al*., 2012). Knowing these figures, as well as keeping in mind that diabetic retinopathy is a biomarker of the underlying widespread effects of abnormal glucose metabolism on the systemic microcirculation (Cheung and Wong, 2008), it is not surprising that patients with

diabetic retinopathy represent a major public health concern. The healthcare costs for patients with diabetic retinopathy complications are almost double of those without the complication, making the societal burden of retinopathy substantial (Heintz *et al*., 2010).

Chronic diabetes is associated with a multitude of macrovascular and microvascular complications, of which retinopathy is only part of the spectrum (Stitt *et al.,* 2016). Some studies reported that retinopathy also predicts poorer survival in persons with type 1 diabetes, but they are associated with concomitant cardiovascular risk factors (Klein *et al*., 1992; Van Hecke *et al*., 2005). Other potential associations in these patients are cerebrovascular disease, heart disease, nephropathy, and systemic vascular complications (Cheung and Wong, 2008). Vision loss due to diabetic retinopathy results from several mechanisms, including macular oedema, macular ischaemia, and fibrovascular contraction secondary to proliferative diabetic retinopathy (Fong *et al.*, 2004).

The rise of morbidity caused by diabetes threatens to overwhelm the stretched healthcare system both in developed nations and in the developing world. Based on the National Diabetes Statistics Report (2014), as the prevalence of diabetes increase, diabetic retinopathy is a major reason of vision impairment affecting approximately 4.2 million people in the world. According to Goh (2008), the prevalence of DR in Malaysia from the 2007 Diabetic Eye Registry was 36.8%. Other than that, the 2007 report on 10,586 diabetics revealed that 63.3% of eyes examined had no DR, 36.8% had any form of DR, of which 7.1% had proliferative diabetic retinopathy while up to 15.0% of eyes had vision threatening DR requiring laser or surgery at their first visit (Goh, 2008).

Proliferative diabetic retinopathy (PDR) is one of the major cause of blindness in the world. According to Danis *et al*. (2008), its development is primarily related to progressive retinal ischemia from diabetic retinopathy, resulting in a compensatory increase of angiogenic growth factors and subsequent of abnormal new blood vessels. Vision loss in patients with PDR frequently results from complications related to fibrovascular proliferation and neovascularization (Fong *et al.*, 1999) and may lead to vision loss, tractional retinal detachment, and vitreous hemorrhage. Pars plana vitrectomy is the surgery of choice in PDR patients with non-clearing vitreous hemorrhaging, tractional retinal detachment (TRD) with or without rhegmategenous retinal detachment, or extensive fibrovascular proliferation. In keeping with advancements in vitrectomy technique, including microincision surgery, the indicators for surgical intervention are now expanding (Gupta and Arevalo, 2013). However, despite the advances in vitrectomy techniques and instrumentation, the anatomical and visual outcomes of vitrectomy are still unpredictable (Gupta *et al*., 2012).

Some factors which have been postulated to affect the outcome include pre-operative vision in the operated eye and contralateral eye, macular involvement, and the use of silicone oil for intraocular tamponade (Yorston *et al*., 2008). However, many more factors which may affect the outcome have yet not been discovered, and the prognosis is complicated by the risk of intra-operative and post-operative complications, which may necessitate repeat surgery (Gupta *et al*., 2012, Yorston *et al*., 2008). For example, Castillo *et al*. (2017) observed that recurrent postoperative vitreous hemorrhaging may occur in a significant proportion of patients and delay the visual rehabilitation.

According to Thompson (2011), there are also some complications related to vitrectomy such as dislocation of cannulas intraoperatively, early postoperative hypotony, choroidal detachment, and possibly and increased risk of infectious endophthalmitis. While, in other study by Ooto *et al.* (2008), they stated that the complications can be more severe, causing large choroidals or escape of gas with inadequate tamponade in eyes with retinal breaks or detachment.

It likely took a few years for retinal surgeons to embrace the new technology of vitrectomy because there were initial concerns regarding higher rates of postoperative complications with the sutureless vitrectomy surgery (O'Reilly and Beatty, 2007). Diabetic retinopathy would be the major public health burden with direct medical costs accounting for $492 million, in addition to lost time and wages related with receiving care (Saadine *et al*., 2008).

1.2 Problem statement

Diabetic affect almost all of the 30 or more cell types in the retina (Stitt *et al.*, 2016). Although the adverse impact on vision is well recognized, the importance of retinopathy signs beyond visual impairment is less well recognized (Frank, 2004). Diabetic vitrectomy surgery is a surgical treatment for diabetic retinopathy that has a very high success rate for improving vision. Patients with PDR have increased from year to year and undergoing vitrectomy is an essential step as a treatment. Data from recent studies showed that patients with PDR complications undergoing vitrectomy have a better visual and anatomical outcomes and reduced number of complications of vitrectomy compared to those not undergoing vitrectomy (Arrigg and Cavallerano, 1998).

Vitrectomy is the mainstay of treatment when sight threatening complications of PDR such as vitreous hemorrhage and tractional detachment develop (Korobelnik *et al*., 2014; Massin *et al*., 2010) Although the majority of vitrectomy surgeries are successful, some patients may still lose visual acuity after a successful surgery. Although few studies have evaluated factors associated with vision loss after vitrectomy surgery, studies investigating the vision loss probability and time to vision loss after vitrectomy among patients with PDR are still lacking (Abougalambou and Abougalambou, 2015).

1.3 Justification of the study

The ability to directly work on or near the retina holds great promise for the future, not only to prevent vision loss, but to restore and enhance the ability to see. Vitrectomy surgery is a highly successful treatment for improving vision post complications of diabetic retinopathy. However, patients may still experience vision loss post vitrectomy surgery. Screening is one of the methods to curb the disease. It allows early detection of retinopathy, is essential in order to initiate prompt treatment of sight threatening retinopathy, and has been demonstrated to be successfull at in preventing vision loss. Providing adequate information to the people about diabetic retinopathy to those affected by diabetes and conducting more convenient screening programmes may increase public awareness and reduce visual loss (Lewis *et al*., 2007).

Secondly, to emphasise that although there have been significant advances in the treatment, there is still a pressing need for better understanding on the basic mechanisms, and timing of vision lost post surgery. This will enable in identifying patients at higher risk and to develop timely post-opearative review schedules thus allowing us to intervene effectively as soon as or before vision loss occurs. In this study, by identifying factors contributing to vision loss after vitrectomy surgery, thus can facilitate intervention planning to prevent vision loss post vitrectomy. Besides that, hopefully from the findings and results of this study will assist clinicians to provide patients with realistic expectations of the visual outcome post vitrectomy surgery.

CHAPTER 2

RESEARCH QUESTIONS, RESEARCH OBJECTIVES AND RESEARCH HYPOTHESES

2.1 Research Questions

1. What is the survival duration of vision loss after vitrectomy surgery among patients with PDR in HRPZ II?
2. What are the differences in survival duration of vision loss after vitrectomy surgery according to socio-demographic characteristics, clinical characteristics, premorbid conditions, and post-operative complications of patients with PDR in HRPZ II?
3. What are the prognostic factors (socio-demographic characteristics, clinical characteristics, premorbid conditions, and post-operative complications) of vision loss after vitrectomy surgery among patients with PDR in HRPZ II?

2.2 General Objectives

To determine the survival duration of vision loss and to identify the prognostics factors of vision loss after vitrectomy surgery among patients with PDR in HRPZ II.

2.2.1 Specific Objectives

1. To determine the survival duration of vision loss after vitrectomy surgery among patients with Proliferative Diabetic Retinopathy in HRPZ II.
2. To determine the differences in survival duration of vision loss after vitrectomy surgery according to socio-demographic characteristics, clinical characteristics, premorbid conditions, and post-operative complications of patients with PDR in HRPZ II.
3. To identify the prognostic factors (socio-demographic characteristics, clinical characteristics, premorbid conditions, and post-operative complications) of vision loss after vitrectomy surgery among patients with PDR in HRPZ II.

2.3 Research Hypotheses

1. The survival duration of vision loss after vitrectomy surgery among patients with PDR in HRPZ II are different according to socio-demographic characteristics, clinical characteristics, premorbid conditions, and post-operative complications.
2. There are significant association between the prognostic factors (socio-demographic characteristics, clinical characteristics, premorbid conditions, and post-operative complications) with vision loss after vitrectomy surgery among patients with PDR in HRPZ II.

2.4 Operational Definition

2.4.1 Visual acuity (VA)

Visual acuity values can be determined by noting the line that the patients can just recognise based on a Snellen chart (see Figure 2.1). The Minimum Angle of Resolution and subsequently its log value (LogMar) is obtained by dividing the denominator by numerator of the Snellen acuity value. (Hajali *et al*., 2009). For example; VA=6/60 then 60 was divided by 6 equals to 10 (Log 10 = 1 LogMar).

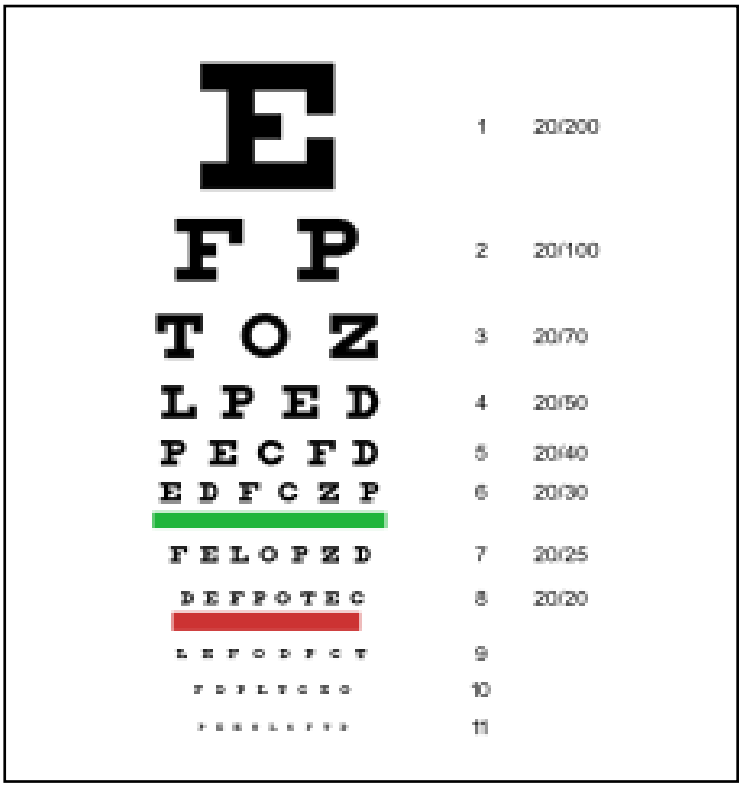

Figure 2. 1: Snellen Chart

2.4.2 Vision loss

Vision loss refers to partial or complete loss of vision. Vision loss also known as vision impairment, is a decreased ability to see to the degree that causes problems not fixable by the usual means, such as glasses. In this study, subjects were considered to have vision loss when the visual acuity post vitrectomy surgery dropped by 0.3 LogMar. This value was used because it represents a worsening of the visual acuity by a factor of two, for example, a drop from vision of 20/20 to 20/40 on a Snellen acuity chart (Hajali *et al*., 2009).

2.4.3 Pars plana vitrectomy (PPV)

Pars plana vitrectomy (PPV) is a surgical procedure that involves removal of vitreous gel from the eye. The procedure derives its name from the fact that vitreous is removed and the instruments are introduced into the eye through the pars plana.

2.4.4 Proliferative Diabetic Retinopathy (PDR)

PDR is the more advanced form of diabetic retinopathy. At this stage, circulation problems deprive the retina of oxygen. As a result, new fragile blood vessels can begin to grow in the retina and into the vitreous, the gel-like fluid that fills the back of the eye. The new blood vessels may leak blood into the vitreous, clouding vision.

2.4.5 Vitreous Hemorrhage

VH is the extravasation, or leakage, of blood into the areas in and around the vitreous humor of the eye. The vitreous humor is the clear gel that fills the space between the lens and the retina of the eye.

2.4.6 Rhegmatogenous retinal detachment (RRD)

RRD occur when the retinal detachment develops due to a retinal break. Fluid from the vitreous cavity, passes through the retinal break into the potential space under the retina, leading to separation of the retina from the underlying choroid.

2.4.7 Tractional retinal detachment (TRD)

TRD which occurs due to pre-retinal membrane formation and scarring that pulls the retina from its attachment.

2.4.8 Neovascularization of iris (NVI)

A medical condition of the iris of the eye in which new abnormal blood vessels (i.e. neovascularisation) are found on the surface of the iris.

2.4.9 Post-operative vitreous hemorrhage (Post-op VH)

Post-operative or recurrent VH is a common complication occurred after vitrectomy. It may occur in association with iris or angle neovascularisation, retinal fibrovascular proliferations, or an anterior hyaloidal fibrovascular proliferation.

2.4.10 Post-operative tractional retinal detachment (Post-op TRD)

Occurs due to pre-retinal membrane formation and scarring that pulls the retina from its attachment after the vitrectomy surgery.

2.4.11 Post-operative epiretinal membrane (Post-op ERM)

An epiretinal membrane is a thin sheet of fibrous tissue that can develop on the surface of the macular area of the retina and cause a disturbance in vision. Most epiretinal membranes happen because the vitreous (the jelly inside the eye) pulls away from the retina. The membrane may also form following eye surgery or inflammation inside the eye.

2.4.12 Post-operative neovascular glaucoma (Post-op NVG)

Post-operative NVG is defined as neovascularization in the anterior segment and intraocular pressure (IOP) $\geq$ 22 mm Hg after vitrectomy.

CHAPTER 3

LITERATURE REVIEW

3.1 Method of Literature Search

Literature were searched using online databases such as Google Scholar, ScienceDirect, PubMed and Scopus for articles from 1980's to 2017 discussing the prognostic factors of vision loss after vitrectomy surgery among patients with PDR. Combinations of the following key words were used: *prognostic factors, risk factors, diabetic retinopathy, proliferative diabetic retinopathy, pars plana vitrectomy, vision loss, tractional retinal detachment, rhegmatogenous retinal detachment, vitreous hemorrhage, diabetes, iris neovascularization and visual loss*. Summaries from the non-English literature were also reviewed.

3.2 Pathophysiology of Diabetic Retinopathy

According to Marques (2015), DR is a common complication of diabetes and is a major cause of visual impairment and blindness in many countries. This visual impairment results from long-term accumulated damage to the small blood vessels in the retina. DR can be defined based on the observation of vascular changes. DR does not cause any symptoms, especially if only one eye is affected. Significant causes of blindness from DR are diabetic macula edema and proliferative diabetic retinopathy (Hendrick *et al.*, 2015). Vascular abnormalities or changes can be recognized by the presence of microaneurysms and small hemorrhages, followed by signs of vascular leakage, such as hard exudates and

larger hemorrhages, vascular dropout, and neovascularization (Marques, 2015). Based on the National Eye Institute (2015) report, diabetic retinopathy may progress through four stages; mild non-proliferative retinopathy, moderate non-proliferative retinopathy, severe non-proliferative retinopathy (NPDR) and proliferative diabetic retinopathy (PDR). In addition, according to Stitt *et al.* (2016), DR can be very broadly classified into two stages which are non-proliferative retinopathy and advanced, proliferative diabetic retinopathy. NPDR can be classified into mild, moderate (more than mild but less than severe NPDR) and severe.

PDR, the more advanced form of the disease will cause new blood vessels to grow into the area of the eye that drains fluid from the eye. This can raise the eye pressure, which damages the optic nerve (American Optometric Association, 2017). PDR can cause vision loss and even blindness if not treated. According to DOCSHOP (2015), 82% of patients that undergoes vitrectomy surgery experience significant improvements in vision after the surgery. However, 18% of patients who had vitrectomy complications, 9% have no improvement in vision while another 9% experience permanent vision loss. The epidemiology of diabetic retinopathy is evolving as prevalence rates increase. Based on a survey by National Health and Nutrition Examination Survey (NHANES) 2008, among adults over 40 years old, 28 % of people with diabetes have DR and 4 % have vision-threatening disease.

PDR is indeed the most common form of vision threatening diabetic retinopathy in Type 1 group patients, but macular edema accounts for most of the vision loss in diabetic patients because it is more common in the more prevalent Type 2 group (Lightman and

Towler, 2003). In addition, according to Wong *et al.* 2001, both non-proliferative and proliferative diabetic retinopathy have now been related to more severe clinical disease such as stroke, coronary heart disease, heart failure and nephropathy. Cheung and Wong (2008), stated that diabetic retinopathy also has been long known to be associated with an increased risk of mortality and principally due to an increase of cardiovascular disease in persons with retinopathy. It is important to note that every patient who develops diabetic retinopathy may experience severe vision loss, which generally occurs only in advanced stages, due to diabetic macula edema and proliferative diabetic retinopathy (Stitt *et al*., 2016).

3.3 The background of Vitrectomy surgery

Vitrectomy surgery, also known as pars plana vitrectomy (PPV), is a surgical procedure that involves removal of vitreous gel from the eye. Pars plana vitrectomy involves the introduction of surgical instruments into the eye through the pars plana and can be defined as the removal of vitreous (American Academy of Ophthalmology, 2015). PPV was first introduced in 1972, when Machemer invented a single port, multifunctional 17-gauge cutter called the vitreous infusion suction cutter (VISC) (Machemer *et al*., 1972). According to a study by Diabetic Retinopathy Vitrectomy Study (1985), 25% of patients undergoing early PPV regained visual acuity of 20/40 or better compared to 15% of patients who underwent conventional treatment.

Based on the study by Ramsay *et al*. (1986), the duration of significant visual loss prior to vitrectomy intervention was less than one month and up to more than six months. The role

of pars plana vitrectomy is still unquestionable for managing complications of proliferative diabetic retinopathy including those that were previously considered blinding. Many favor early vitrectomy as it gives better results and better visual outcomes, due to advances in surgical and pharmacologic assisted technique (Gupta *et al*., 2012). PPV is indeed the best option for the patients to treat the complication of proliferative diabetic retinopathy.

The first 3-port, 20-gauge vitrectomy system (standard system) in which the sclerotomies and conjunctiva were saturated after the procedure was the standard in vitrectomy surgery since the mid-1970s and later in 2002, 22-gauge vitrectomy system were introduced (Wubben et al., 2016). This was followed by the introduction of a 23-gauge and a 27-gauge sutureless vitrectomy system (Eckardt *et al*., 2005; Oshima *et al*., 2010). Overall, there is an increase in the vitrectomy rates per 1000 enrollees over the past decade (Wubben *et al*., 2016). Many of the studies using the small gauge vitrectomy also found decrease inflammation and pain postoperatively and improved patients comfort (Kellner *et al*., 2007; Romero *et al.,* 2006). Other studies also reported that small gauge vitrectomy has been used successfully for a wide variety of vitreoretinal surgical indications (Tan *et al.,* 2008; Spirn *et al.,* 2009). The reduction in the incision size has led to minimization of tissue trauma, postoperative convalescence period, less postoperative inflammation, and faster recovery (Nagpal *et al*., 2012).

3.4 Median Time or survival duration of Vision Loss

A retrospective study by Gupta *et al*. (2012) of the patients undergoing PPV from January 1999 to May 2010 found that out of 249 patients, 95.3% of eyes had a flat retina (retina still not functioning properly post-surgery) at final follow-up. According to this study, they found that the median time was 14 months with mean 1.44 (SD:1.88 years). According to Rice *et al*. (1983), the cumulative incidence of neovascular glaucoma (NVG) occurred in the first few months after vitrectomy with a median time of six months. The estimated relative risk of neovascular glaucoma for eyes underwent vitrectomy was 4.6 with a 95% CI from 1.5 to 13.7.

The post-operative complications primarily occurred the first year after surgery. The most frequent postoperative complication was vitreous hemorrhage and tractional retinal detachment. For VH, the median probability time was estimated to be in three months after vitrectomy for visual acuity less than 0.1 LogMar unit pre-operatively of operated eye (Ostri *et al*., 2014). Other than that, this study also determined the median probability time of vision loss for prognostic factor post- operative TRD was 12 months (including use of silicone oil in surgey). However, there was no significance difference in risk of operated eye for post op TRD (P-value=0.07) with median time was 5.6 months and mean time was 10.5 months (SD:19.2 months) (Hwang *et al*., 2013).

3.5 Prognostic factors of vision loss after vitrectomy surgery

3.5.1 Socio-demographics and clinical characteristics

Most patients who develop severe vision loss after vitrectomy have proliferative diabetic retinopathy (Davis *et al.,* 1998). Based on the study by Ramsay *et al*. (1986), the duration of significant vision loss prior to vitrectomy intervention was less than one month and would differ according to each patient which some will have vision loss in one to three months, three to six months, and more than six months. DR represents a major socioeconomic status problem with around 2% of diabetic patients becomes legally blind while 10% have a severe visual handicap because of PDR, despite the availability of several effective therapeutic treatment such as laser photocoagulation or vitrectomy (Zhang *et al*., 2009).

The incidence of vision loss or blindness increase significantly with age in both younger and older onset in taking insulin group. This trend approaches significance with P-value = 0.051 in the older onset group not taking insulin. The vision loss was associated with age (younger onset: $P<0.001$, older onset: $P<0.001$). The rate of blindness increases significantly only in the younger onset group when the duration increase (Moss *et al*., 1988). However, according to Moss *et al*. (1988), both not significant in older onset and younger onset with $p = 0.26$ and $p = 0.81$ respectively. Longer in duration of diabetes and more severe retinopathy were associated with the development of proliferative diabetic retinopathy in younger group. Because of the presence of PDR, it was associated with an increased 4-year risk of loss of vision, cardiovascular disease, diabetic nephropathy, and mortality (Klein *et al*., 1992). In another report by Moss *et al,* (1988), with the increasing

in duration of diabetes, increased the blindness in younger onset persons and older onset persons taking insulin.

The rate of occurrence of visual loss after vitrectomy tended to be higher in higher in persons 50 years of age or older in person with Type 2 diabetes, in women, visual acuity impairment, and macular edema (Davis *et al*., 1998). The results were estimated using multivariate discrete Cox models, proving that baseline visual acuity remained a significant factor with odds ratios were approximately 1.5 and 2 or more. Univariate models were constructed in which older age, female gender, type 2 diabetes, decreased visual acuity, and macular edema were all nominally significant risk factors, and increased body weight was of borderline significance (Davis *et al*., 1998).

Type 1 DM is characterised by beta cell destruction caused by an autoimmune process, leading to absolute insulin deficiency while most individuals with type 2 DM exhibit intra-abdominal obesity which related to the presence of insulin resistance (Baynest, 2015). This is the most common form of DM and highly associated with a family history of diabetes, older age, obesity and is also common in women (Massin, 2001). Insulin is the mainstay of treatment for Type 1 patients. For Type 2 patients, when blood glucose levels cannot be controlled by diet, weight loss and oral medications, insulin is also crucial (Valera Mora *et al.*, 2003). In contrast, based on the study by Zhang *et al.* (2009), they hypothesized that long-term insulin therapy maybe deteriorates PDR. This is because when insulin contacts with retinal vascular endothelium and stimulate VEGF and other

growth factor, it will increase retinal vascular permeability resulting in more serious retinal edema.

Central vision may be impaired by macular edema or capillary nonperfusion. New blood vessels of PDR and contraction of the accompanying fibrous tissue can distort the retina and lead to tractional retinal detachment that can produce severe and often irreversible vison loss. Moreover, the new blood vessels also can cause bleeding, adding the further complication of pre-retinal or vitreous hemorrhage (Fong *et al*., 2004). According to El Annan and Carvounis (2014), diabetic VH secondary to PDR is a cause of severe vision loss in diabetic patients. Combined tractional and rhegmatogenous retinal detachment (combined RD) is a rare but serious complication in PDR and most of cases undergoing PPV for complications of diabetic retinopathy had pre-operative combined RD (Hsu et al., 2014). Pre-operative neovascularization of the iris (NVI) or also known as rubeosis iridis can cause neovascular glaucoma which is a severe ocular complication of PDR (Fernandez-Vigo *et al*., 1997). While according to Mishra *et al*. (2013), NVG is a severe form of glaucoma characterized by iris neovascularization, a closed anterior chamber angle, and extremely high intraocular pressures (IOP) along with severe ocular pain and poor vision.

3.5.2 Premorbid condition

Losing 3 lines in visual acuity is an important event and would mean that one with initially normal vision would have difficulty with small print or figures. This related to hypertension in which the proportion of patients who lost this degree of visual acuity was significantly higher in the less tight BP control group (higher blood pressure) compared with the tightly controlled BP group (lower blood pressure) (Matthews *et al*., 2004). Hypertension is also a major risk factor for the development of other retinal vascular diseases, such as retinal vein and artery occlusion. Based on the study of randomised clinical trial, adequate controlled of blood pressure can reduce vision loss associated with diabetic retinopathy (Wong and Mitchell, 2007). PDR was associated with the incidence of stroke mortality in both Type 1 and Type 2 diabetes independent of diabetes duration, glycemic control, and other risk factors (Klein *et al.*, 2004).

Risk of heart disease increase as increased in total cholesterol ($P < 0.001$), LDLC ($P = 0.04$), and triglyceride ($P = 0.001$) levels that were associated with a more rapid onset of obvious retinal hard exudate. Patients were at a higher risk of losing visual acuity with the extent of hard exudate even after adjusting for the extent of macular edema (Chew *et al*., 1996). However, according to Greenberg *et al*. (2016), the relationships between vision loss and future stroke/myocardial infarction (adjusted HR 1.51, 95% CI 0.78–2.90) were no longer significant.

A study shows that compared to patients without diabetic retinopathy, patients with retinopathy are more likely to sustain major adverse cardiac events or complications, for example; death, myocardial infarction, heart failure even after factoring effects of age, gender, diabetes duration, insulin use, and other factors that may affect prognosis after these procedures (Briguori *et al*., 2005; Ono *et al*., 2006). Eyes with advanced microvascular disease may be particularly susceptible to decreasing in perfusion, leading to worsening or macular ischemia and this explained postoperative vision loss in patients with diabetic retinopathy (Jain et al., 2012).

The results show the association of chronic kidney disease (CKD) with visual impairment (VI), while the odds of VI increased with increasing severity of CKD. In multivariable models, CKD was significantly associated with visual impairment with odds ratio = 1.34, 95% confidence interval (1.14–1.58), and P-value = 0.001 (Wong *et al*., 2016). Other than that, a research by Lin *et al.* (2014) reported that on patients with kidney disease, the creatinine level was significantly higher in the study group (which postoperative VA is worse than preoperative VA) (4.07 ± 4.15 mg/dL) than in the control group (which postoperative VA is better than preoperative VA) (1.23 ± 0.46 mg/dL; p = 0.003). The data in this study showed that the patient's creatinine level was significantly related to the outcome of surgery for PDR.

3.5.3 Post-operative complications

The incidence of vision loss was associated with the presence of macular edema, in younger onset, $p < 0.001$ and also in older onset, $p < 0.001$. Macula edema were thought to be sufficient to cause the visual acuity reduction in the absence of other causes (Moss *et al*., 1988). Postoperative vitreous hemorrhage following PPV for PDR has been reported in 12% - 63% of cases and may occur within the first few weeks or even months later after the surgery (Yang 1998; Novak *et al*., 1984; Schachat *et al*., 1983). The study by Khutaila *et al*., (2013), defined the rate of postoperative VH and reoperation after initial vitrectomy and examined associated risk factors after 23-gauge PPV in eyes with nonclearing VH resulting from PDR. The study also reported that that 32% of eyes develop vitreous hemorrhage following 23-gauge PPV for diabetic retinopathy. Postoperative ophthalmic variables associated with a poor outcome in this study included persistent or recurrent VH which showing significant relationship with P-value = 0.003 (Unver *et al*., 2009).

According to Wang et al. (2014) in his study, vitreous hemorrhage occurred in 14 eyes with the incidence of 4.6% after vitrectomy. VH appeared in postoperative after day one up to over six months. The cause of postoperative vitreous hemorrhage would be the residual neovascular membrane, insufficient photocoagulation range and intensity, neovascularszation, and instable blood glucose level. Postoperative problems that affecting vision loss specifically recorded included persistent vitreous hemorrhaging (present from postoperative day 1 until beyond 90 days) and recurrent vitreous hemorrhaging (after an observed period of clearing (Castillo *et al.*, 2017). The surgical

management for PDR-related is the most challenging procedures encountered as the complication of VH after vitrectomy (PPV) is the most reported as high as 75 % (Tolentino *et al.,* 1989). Common complications after vitrectomy include corneal epithelial defects, cataract, recurrent VH, iatrogenic retina breaks, rhegmatogeneous retinal detachment and neovascular glaucoma (Yorston et al., 2008).

From the study by Unver *et al*., (2009), eight out of the eyes that developed post-operative rubeosis iridis had recurrent retinal rhegmatogenous detachment (RRD), significant with $p < 0.001$ by using logistic regression. Therefore, in univariate analysis, the significant factors for a final visual acuity of less than 5/200 were recurrent RRD which produced a relative risk of 64.8. 63% of all post vitrectomy patients achieved a final visual acuity of 20/200 or better. Worsen visual acuity which was the hand motion were in the patients with recurrent retinal detachment after unsuccessful vitrectomy at the time of initial surgery (Blodi *et al*., 1992). According to Castillo *et al*. (2017), recurrent retinal detachment was found (development after an observed period of fully attached retina) and new retinal detachment have occurred in an eye that did not previously have a retinal detachment after the patients undergoing vitrectomy. Recurrent tractional retinal detachment (TRD) was also a predictor for poor visual outcome.

By using logistic regression, recurrent TRD reported to be a significant predictor of vision loss with $P = 0.02$ (Unver *et al*., 2009). Based on the same study by Blodi *et al*. (1992), showed that after vitrectomy, three patients had new retinal detachments within 6 months after vitrectomy. In other study, combined traction and rhegmatogenous retinal detachment was found in seven of 10 eyes (70%) in the study group (postoperative VA is