Analysis of the Secondary Endpoints of the SPR Study using Competing Risk Models

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ANALYSIS OF THE SECONDARY ENDPOINTS OF THE SCLERAL BUCKLING AND PRIMARY VITRECTOMY (SPR) STUDY USING COMPETING RISK MODELS

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Thesis submitted in partial fulfilment of the requirements for the Degree of Master of Science in Applied Statistics.

(2006-2007)

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Firstly, I appreciate the good Lord who gave me the courage, inspiration and will power to handle a task of this magnitude. At the start, I wondered whether I could do a research using competing risk models without having undergone the usual classroom tutorship on competing risk analysis. I had always believed the "I can and I will" principle taught me by my dad, David. I thank my dear wife Elizabeth for giving me the much needed emotional support and for her understanding when I had to lock up myself several times in my study.

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I give kudos to Professor Paul Janssen for the painstaking effort to help me write a report that conveys my ideas in an easily digestible way to facilitate understanding by all and sundry. Without his generous contributions you may find the text more difficult to understand.

Lastly to all readers of this report I say thank you for the interest in reading my report and wish you good understanding of it.

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ABSTRACT

The Scleral Buckling and Primary Vitrectomy (SPR) study is an European multicenter clinical trial where patients with a type of retinal detachment (caused by a break, tear or hole in the retina) called rhegmatogenous retinal detachment (RRD) were randomized into one of two surgical methods of treatment (scleral buckling or primary vitrectomy method) in each of two subtrials. The subtrials, which consist of two groups of patients according to the state of their eye lens is either the aphakic (artificial lens) or the phakic (natural lens) group. The study recorded the time of the occurrence of three events of interest, the proliferative vitreoretinopathy (a post operation complication in the retina), retina re-detachment and re-operation.

The purpose of the study was to determine the more effective of the two methods in the treatment of rhegmatogenous retinal detachment of medium complexity.

Survival analysis using one of the three events at a time was carried out to study the differences in the risk of each event between the two treatment groups for each subtrial. This was followed by a competing risk analysis using the log-rank and Gray's test. The event of re-operation was taken as competing with the other two events.

The results of the 'one-event at a time' survival analysis and that of the competing risk analysis were similar. The competing risk analysis when the event of interest was proliferative vitreoretinopathy revealed that the aphakic patients treated with either method have similar or same risk of the post-operative incidence of proliferative vitreoretinopathy both in the absence (p=.327) and presence(p=.305) of competing risk of re-operation and they also have same risk of experiencing a re-operation (p=.721). However, for the phakic patients, the risk of having re-operation was found to be higher for patients treated with primary vitrectomy (p=0) than with scleral buckling. There also was no significant difference in the risk of experiencing proliferative vitreoretinopathy both in the absence (p=.67) and presence (p=.675) of the re-operation, the competing event.

When the event of interest was retinal re-detachment, the result show that for the aphakic patients, the risk of retinal re-detachment was higher for patients with scleral buckling both in the absence (p=.0054) and presence (p=.0048) of the

competing risk of re-operation but patients treated with either method experienced the same risk of re-operation. For the phakic patients, there was no significant difference in the risk of retinal re-detachment both in the absence (p=.078) and presence (p=.081) of the competing risk of re-operation.

Conclusively, it was found that primary vitrectomy was more effective for the aphakic patients and scleral vitrectomy was more effective for the phakic patients.

CHAPTER ONE

1.0 INTRODUCTION

1.0.1 Medical background / background information

An eye disease called rhegmatogeneous retinal detachment (RRD)[1] occurs as a result of a break, tear or hole in the retina allowing fluids from the vitreous humour to enter the potential space beneath the retina. This causes the retina to separate from the layer beneath and an individual with this condition will often experience often experience flashes of light, floaters and a curtain-like loss of vision as the situation deteriorates (EyeMDlink.com and its content providers, 2006). This type of detachment called Rhegmatogenous Retinal Detachment (RRD) represents an emergency, and surgery is typically scheduled urgently (EyeMdlink.Com and its content providers, 2006).

The annual incidence is approximately 1 in 10,000 or about 1 in 300 over a lifetime (Haimann, 1982) mostly in persons aged 40 to 70 years. Some of the risk factors of RRD are myopia[2], cataract surgery, diabetic retinopathy[3] and traumatic injury to the eye (www.visionchannel.net).

Surgery is employed to treat rhegmatogenous retinal detachment and two most popular methods are Scleral Buckling and Primary Vitrectomy[4]. Generally, the scleral buckling method uses silicone sponge, rubber or semi hard plastic that the ophthalmologist places on the outer layer of the eye (the sclera, or the white of the eye). The material is sewn to the eye to keep it in place and the buckling element usually left in place permanently. This "buckles" the sclera toward the middle of the eye thereby relieving the pull on the retina and allows the retinal tear to settle against the wall of the eye. The buckle effect may cover only the area behind the detachment, or it may encircle the eyeball like a ring. On the other hand, primary vitrectomy involves removal of the vitreous humour. It allows the ophthamologist better access to the back of the eye. The surgeon inserts small instruments into the eye, cuts the

[1] The term rhegmatogeneous is derived from the Greek word rhegma, which means a discontinuity or a break. Section A.0 in the appendix shows the retinal and other interior parts of the human eye
[2] Nearsightedness
[3] Diabetic retinopathy is a damage to the retina caused by complications of diabetes mellitus (high blood sugar).
[4] Section A.1 in the appendix contains the procedure for the scleral buckling and primary vitrectomy followed for the present study.

vitreous gel, and suctions it out. Then he may treat the retina with laser (photocoagulation), remove fibrous or scar tissues, flatten areas where the retina has become detached, or repair tears / holes in the retinal. At the end, silicon oil or a gas (Sulphur Hexafluoride, SF_6) is injected into the eye to replace the vitreous gel and restore normal pressure in the eye (www.webmd.com/eye-health).

1.0.2 Motivation for the study

Presently, there are few scientific facts to say either of the two surgical methods gives comparative advantage over the other. Most surgeons look at the anticipated level of difficulty of the situation to choose the method to use. Moreover, both methods have their shortcomings and there is no guarantee that the retinal would not re-detach sooner or later. This leads us to the study objective.

1.0.3 Objective of the study

Clearly, the study objective is to determine the better or more effective of the two methods in the treatment of rhegmatogenous retinal detachment of medium difficulty. In view of this, the scientific question to answer would be "is there a difference in treatment effect, as determined from the survival[5] experience of the patient, between those treated with scleral buckling and those treated with primary vitrectomy method?"

1.0.4 Brief description of Methods to be used

To answer the scientific question, we shall make use of some endpoint criteria like time to occurrence of a re-operation, time to the occurrence of retinal re-detachment and time to the occurrence of an associated retina post-surgery complication called proliferative vitreoretinopathy. These three events just mentioned are defined briefly below:

1) re-operation: this refers to revision of any aspect of the same operation method that was done in the first instance. The variable representing re-operation in the data set used for the analysis is 'ReOPs', which has a yes / no response and the variable 'TimeReop' records the time when a re-operation occurred (tables

[5] Survival here refers to the length of time the patient stays free of the condition after surgery is done.

1.0 and 1.1 give more information). Possible re-operations are, for example: laser coagulation, cryopexy, membrane peeling, revision of vitrectomy or scleral buckling. As much as it was possible re-operation was of the same type as the one randomly assigned initially.

2) Retinal re-detachment as the name implies occurs when the retinal separates from the beneath layer again after initial surgery. 'Reamotiones'[6] is the variable indicating the occurrence of retinal re-detachment and 'TimeReamo records the time it occurred (in the dataset used: tables 1.0 and 1.1).

3) Proliferative vitreoretinopathy (PVR)[7], despite the long name, is simply scar tissue formation within the eye. In PVR, scar tissue forms in sheets on the retina, which contract. This marked contraction pulls the retina toward the center of the eye and detaches; this distorts the retina severely (http://www.retinatexas.com/vitreoretinopathy.html) Fig.a.2 in the appendix shows a retinal detachment with PVR. 'PVR_B or C' in the dataset records the occurrence of a PVR of stage B or C and 'TimeBorC' is the time PVR B or C occurred (please refer to tables 1.0 and 1.1).

The analyses of time-to-event data is usually referred to as survival analysis and the event does not necessarily have to be death but any event that occurs over time, such as the three mentioned above, relapse of disease or even discharge from hospital. The application of the principles of survival analysis is widespread (in engineering[8], marketing, management and in many other disciplines). A more general term would be 'failure time analysis'. The time to the event of interest is analyzed basically by comparing the survivor functions of the groups or levels of a variable for significant differences and / or by modeling the hazard of the distribution of the survivor function. However, when we are interested in the behaviour of a particular event of interest in the presence of other possible or competing events, then we have the situation of analyzing the distribution of time to first occurring events. Hence we have a competing risk situation. Pintilie (2006) discussed that a competing risk situation arises when an individual can experience more than one type of event and the occurrence of one type of event hinders the occurrence of the other types of

[6] Also referred to as reamotio in this report
[7] "Proliferative" because cells proliferate and "Vitreoretinopathy" because the problems involve the vitreous and retina. PVR is graded according to the degree of complication and this report talks about PVR stage B or C.
[8] For example in the study of strength of materials.

events. We are only interested in the first to occur even when the other events still occurred after the first.

This research study majorly made use of competing risk analysis to study the competing nature of the three events above in order to evaluate the supremacy of one of the two surgical methods over the other.

1.1 REVIEW OF THE RESULT OF THE SPR STUDY BY DR. HEINRICH HEIMANN[9] (PRESENTED IN MAY 2006)

The SPR study is a prospective randomized European multi-center clinical trial named the Scleral Buckling Versus Primary Vitrectomy in Rhegmatogenous Retinal Detachments Study (SPR Study) and conducted in 27 centers in Austria, France, Germany, UK, Sweden and Switzerland. There were two subtrials or subgroups, phakic[10] and pseudophakic / aphakic based on the state of the lens of the patient's eye. Randomization to either the scleral buckling treatment arm or primary vitrectomy was done in each of the subgroups separately.

The phakic group had 416 patients and pseudophakic / aphakic group had 265 patients. The main endpoint was defined as change in visual acuity at 12-month follow-up. The secondary endpoints were primary success without retina affecting reoperations, number of reoperations and cataract surgeries (phakic groups), PVR rate and final anatomical success rates.

The result revealed that although there was no significant difference in visual acuity between the treatment arms for each of the two groups, the re-detachment rates in the pseudophakic/aphakic group was much higher for those treated with scleral buckling surgeries. However, it was a little lower for patients treated with scleral buckling surgeries under the phakic subtrial. In the phakic subtrial, patients who were treated with scleral buckling surgery had significantly fewer cataract operations during follow-up (P<.00005). No significant differences were found within the pseudophakic/aphakic subtrial for final anatomical success (P=.9078) and PVR Grade B or C (P=.1879). In the phakic subtrial, comparison of primary as well as final anatomical success did not show significant difference (P=.9137 and P=.8634,

[9] Heinrich Heimann, MD, is a consultant ophthalmic surgeon, St Pauls Eye Unit, Royal Liverpool Hospital, Liverpool, UK. heinrichheimann@yahoo.de

[10] 'Phakic' describes the state of an eye that still has its natural (crystalline) lens intact. So an eye that still contains its natural lens is called phatic eye. The opposite is aphakic or pseudophakic

respectively), nor did comparison of PVR rates (P=.1938) or number of retina-affecting reoperations (P=.1269).

In summary, Dr. Heimann and colleagues found no difference between scleral buckling surgery and primary vitrectomy regarding the main endpoint in pseudophakic as well as phakic patients. They noted that, based on the analysis of secondary endpoints, primary vitrectomy combined with scleral buckling is recommended in pseudophakic/aphakic patients. Scleral buckling is recommended in phakic patients. *Reference site: www.retinatoday.com*

For the present analysis, we are critically going to study whether re-operation influences the time to occurrence of the post-operative incidences of PVR stage B or C and retinal re-detachment for patients treated with the two methods in each subgroup separately. Hence re-operation is seen as the event competing with each of the other two and the other two events are not competing with each other. The motivation for re-operation as the competing event is easily seen in the sense that it could prevent the occurrences or change the probability of occurrences of the other two events and as well from our data. When some patients had re-operation, they did not experience any of the other two events.

1.2 DATASET AND THE PRESENT ANALYSIS

Theoretically, the study was proposed to end after one year but there were many patients that had study times as high as 3 to 4 years for one reason or the other. The original dataset, which is not shown here for its size, consists of 205 variables and 3261 observations of 681 patients. Observations per patient ranged from 4 to 11 denoting the number of times the patient was visited until the study closed or the patient was lost to follow up. The types of variables in the original dataset are patient ID, gender, no of operated eye, operation type and date, events occurring and time of occurrence, state of the eye, macular medical history and many other characteristic variables of the eye. Only 12 variables from the original dataset were relevant to our analysis and are shown in table 1.0 (*without asterisks*). The other 13 variables (with *asterisks*) were derived from the information provided by the 12 (*they shall be useful for the subsequent analysis*). Therefore our final dataset consists of 25 variables for the 681 patients. Table 1.1 describes the meaning of each variable.

Table 1.0 SPR study: some datalines for 14 patients

PatNr	subtrial	Sex	OP	SurgD	V4D	PVR_BoderC
11001	aphakic	male	Scleral buckling	15-Dec-98	21-Dec-99	No
11002	aphakic	female	Primary vitrectomy	23-Dec-99	19-Dec-00	Yes
11003	aphakic	male	Primary vitrectomy	31-Mar-00	6-Apr-01	Yes
11004	aphakic	male	Scleral buckling	26-May-00	25-May-04	No
11005	aphakic	female	Scleral buckling	30-May-00	29-May-01	No
11006	aphakic	male	Primary vitrectomy	21-Jun-00	28-Jun-00	No
11007	aphakic	male	Scleral buckling	7-Jul-01	12-Jul-02	No
11008	aphakic	female	Primary vitrectomy	21-Sep-01	20-Sep-02	No
11009	aphakic	male	Primary vitrectomy	10-Oct-01	16-Mar-02	No
11010	aphakic	male	Scleral buckling	9-Jan-02	17-Jan-03	No
11011	aphakic	male	Primary vitrectomy	11-Jan-02	26-Sep-02	No
11021	aphakic	male	Scleral buckling	7-Aug-00	9-Oct-01	No
12001	phakic	female	Primary vitrectomy	3-Mar-99	9-Mar-00	No
12002	phakic	male	Scleral buckling	11-Mar-99	21-Mar-00	No

Table 1.0 SPR study: some datalines for 14 patients. Continued

PatNr	PVRD	ReOPs	firstReOPD	Reamotiones	firstReAmotioD	TimeReop*
11001		Yes	15-Dec-98	Yes	15-Dec-98	371
11002	25-Feb-00	Yes	18-Apr-00	No		117
11003	26-May-00	Yes	25-Apr-00	No		25
11004		No		No		1460
11005		Yes	4-Jun-00	Yes	4-Jun-00	5
11006		No		No		7
11007		Yes	7-Jul-01	Yes	7-Jul-01	370
11008		No		No		364
11009		No		No		157
11010		No		No		373
11011		Yes	11-Jan-02	Yes	11-Jan-02	258
11021		Yes	7-Aug-00	Yes	7-Aug-00	428
12001		Yes	7-Dec-99	No		49
12002		No		No		364

Table 1.0 SPR study: some datalines for 14 patients. Continued

PatNr	CensReop*	TimeBorC*	CensBorC*	TimeReamo*	CensReamo*	Firsteventtime*
11001	1	371	1	0	0	0
11002	0	64	0	362	1	64
11003	0	56	0	371	1	25
11004	1	1460	1	1460	1	1460
11005	0	364	1	5	0	5
11006	1	7	1	7	1	7
11007	1	370	1	0	0	0
11008	1	364	1	364	1	364
11009	1	157	1	157	1	157
11010	1	373	1	373	1	373
11011	1	258	1	0	0	0
11021	1	428	1	0	0	0
12001	0	366	1	49	0	49
12002	1	364	1	364	1	364

Table 1.0 SPR study: some datalines for 14 patients. Continued

PatNr	Firstevent*	MargPVR*	MargReamo*	MargReop*	EvtNoReamo*	EvtNoPVR*
11001	2	0	1	0	0	2
11002	1	1	0	0	1	0
11003	3	0	0	1	3	3
11004	0	0	0	0	0	0
11005	2	0	1	0	0	2
11006	0	0	0	0	0	0
11007	2	0	1	0	0	2
11008	0	0	0	0	0	0
11009	0	0	0	0	0	0
11010	0	0	0	0	0	0
11011	2	0	1	0	0	2
11021	2	0	1	0	0	2
12001	2	0	1	0	0	2
12002	0	0	0	0	0	0

Table 1.1: SPR study: description of variables in the dataset

Variable name	Description
PatNr	Patient identity number
Subtrial / subgroup	Aphakic / phakic eye condition of patient
Sex	Gender (male / female)
OP	Randomized treatment: primary vitrectomy & scleral buckling
SurgD	Date of surgery
V4D	Date of last visit
PVR_BoderC	Incidence of post-operative PVR grade B or C (yes / no)
PVRD	Date of occurrence of PVR stage B or C
ReOPs	Incidence of re-operation (yes / no)
FirstReOPD	Date first re-operation
Reamotiones	Incidence of retinal re-detachment (yes / no)
FirstReAmotioD	Date of first retinal re-detachment
TimeReop*	Time to first re-operation (days)
CensReop*	Censoring indicator for re-operation (1 if reoperation, 0 if censored)
TimeBorC*	Time to occurrence of PVR B or C (days)
CensBorC*	Censoring indicator for PVR (1 if PVR BorC, 0 if censored)
TimeReamo*	Time to first retinal re-detachment (days)
CensReamo*	Censoring indicator for re-detachment (1 if detached, 0 if censored)
Firsteventtime*	Time to occurrence of first of the three events (days)
Firstevent*	Censoring indicator for first event (1 if PVR was first, 2 if re-detachment was first, 3 if re-operation was first and 0 if no event at all.
MargPVR*	Censoring indicator for the marginal distribution of PVR event (1 if first event was PVR, 0 otherwise)
MargReamo*	Censoring indicator for the marginal distribution of re-detachment (1 if first event was re-detachment, 0 otherwise
MargReop*	Censoring indicator for the marginal distribution of re-operation (1 if first event was re-operation, 0 otherwise)
EvtNoReamo*	Indicator variable (1 if first event is PVR, 3 if first event was re-operation and 0 otherwise)
EvtNoPVR*	Indicator variable (2 if first event was re-detachment, 3 if first event was re-operation and 0 otherwise

CHAPTER TWO

2.0 BASIC CONCEPTS OF SURVIVAL DATA ANALYSIS

According to Collett (1994), "survival analysis is the phrase used to describe the analysis of data that correspond to the time from a well-defined time origin until the occurrence of some particular event or end-point." In medical research, the time origin will often correspond to the recruitment of an individual into an experimental study, such as a clinical trial to compare two or more treatments (Collett, 1994).

However, it is not always the case that the event(s) of interests occur as at the time the study ended. The survival time of an individual is said to be censored when the end-point of interest has not been observed for that individual (Collett 1994). Some causes of censoring are: termination of study, death due to a cause unrelated to the event of interest, loss to follow-up, etc. Types of censoring are right, left and interval censoring but right censoring is the most common. A patient who entered a study at time t_0 dies at time $t_0 + t$ but t is not known either because the individual is still alive or because he or she has been lost to follow up. If the individual was last known to be alive at time $t_0 + c$, the time c is said to be a censored survival time. This censoring occurs after the individual has been entered into the study, that is, to the right of the last know survival time, hence called right censoring. The present study deals with right censoring.

The survival time, X for an individual is the minimum of the pair (T,C) where T is the event time and C the censoring time. Mathematically,

X = min (T,C) and the censoring indicator, δ is given by

$$\delta = \begin{cases} 1, \text{ if } X = T \text{ and} \\ 0, \text{ if } X = C. \end{cases}$$

This means that when then the failure time indicator is 1 we observe the event time, otherwise we observe the censoring time.

There are two reasons why standard statistical procedures used in data analysis cannot be directly applied to survival data: 1) Survival data are generally not symmetrically distributed (tends to be positively skewed) and 2) They are frequently censored.

2.0.1 SURVIVOR AND HAZARD FUNCTION

T_i the event time for an individual is a random variable having a probability distribution with underlying *probability density function, f(t).* The probability of the failure time occurring at exactly time T_i (out of the whole range of possible T's) if T is *continuous* is,

$$f(t) = \lim_{\Delta t \longrightarrow 0} \frac{P(t \le T < t + \Delta t)}{\Delta t}.$$

The cumulative distribution function of T is then given by

$F(t) = P(T \le t) = \int_0^t f(u)du$,

and this means that the survival time is less than or equal to some value t. We now define the survivor function to be the probability that the survival time is greater than or equal to t, hence

$$S(t) = 1 - P(T \le t) = 1 - F(t).$$

Example: If t = 60 years, S(t = 60) = probability of surviving beyond 60 years.

For a *discrete* random variable, T (suppose that T takes values in a_1, a_2, a_3, …, a_n), the density function is given by

f(t) = P(T = t)

$$= \begin{cases} f_j & \text{if } t = a_j,\ j = 1, 2, \ldots, n \\ 0 & \text{if } t \neq a_j,\ j = 1, 2, \ldots, n \end{cases}$$

and

$$S(t) = \sum_{u \ge t} f(t) = \sum_{a_j \ge t} f(a_j) = \sum_{a_j \ge t} f_j .$$

The *hazard function*[11] sometimes called instantaneous failure rate for continuous random variables is given by

$$h(t) = \lim_{\Delta t \longrightarrow 0} \frac{P(t \le T < t + \Delta t / T \ge t)}{\Delta t}.$$

$$\text{Hazard from density and survival}: h(t) = \frac{f(t)}{S(t)} .$$

[11] Also known as the conditional failure rate in reliability, the force of mortality in demography, the intensity function in stochastic processes, the age-specific failure rate in epidemiology, the inverse of the Mill's ratio in economics, or simply as the hazard rate (Klein and Moeschberger, 1997)

In words: the probability that ***if you survive to t***, you will succumb to the event in the next instant. According to Collett (1994), "the hazard function is the probability that an individual dies at time t, conditional on he or she having survived to that time". This explains why it is called instantaneous failure rate.

Cumulative hazard function, for continuous random variables is given by
$\wedge(t) = \int_0^t h(u)du$.

For a ***discrete random variable***, T (again, suppose that T takes values in a_1, a_2, a_3, …, a_n), the hazard function is given by

$$h(a_j) \equiv h_j = P(T = a_j \mid T \geq a_j)$$
$$= \frac{P(T = a_j)}{P(T \geq a_j}$$
$$= \frac{f(a_j)}{S(a_j)}$$
$$= \frac{f(t)}{\sum_{k:\, a_k \geq a_j} f(a_k)}.$$

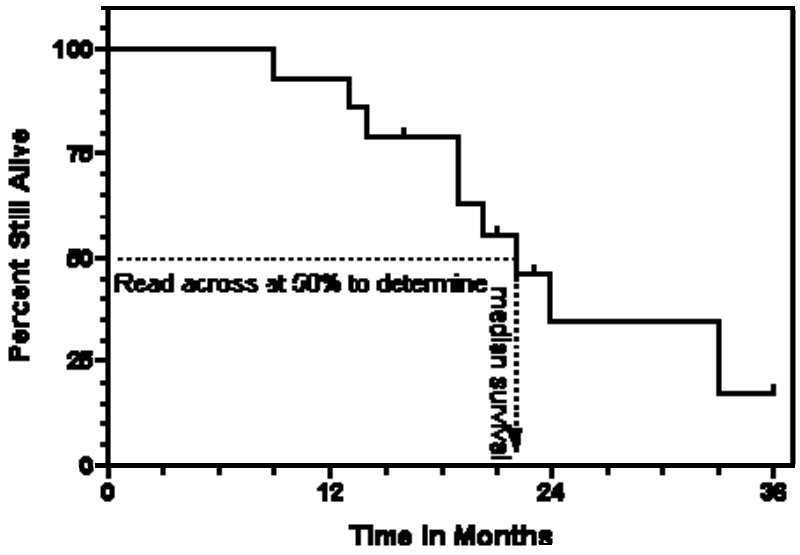
Cumulative hazard function is given by

$$\wedge(t) = \sum_{k:\, a_k < t} h_k \ .$$

2.0.2 MEASURING CENTRAL TENDENCY IN SURVIVAL ANALYSIS

The median is the preferred summary measure of the location of the distribution of survival time since the survival time distribution tends to be positively skewed (Collett, 1994). The median survival time is the time beyond which 50% of the individuals in the population under study are expected to survive. In other words, half of the population under study has not experience the event of interest beyond the median time: half the subjects have died and half are still alive.

It is noteworthy to say that If fewer than half the subjects have died by the end of the study, you cannot determine median survival.



Source: http://www.graphpad.com/www/book/survive.htm

Fig. 2.0 typical survival curve showing how to read the median time.

2.0.3 ESTIMATING THE SURVIVOR FUNCTION

There are parametric and non-parametric methods of estimating the survivor function. The parametric methods involve specifying a model for S(t) based on a particular density function f(t) whereas the non-parametric estimation involves developing an empirical estimate of the survival function.

If no censoring, then we have the empirical survival function, given by

$$\hat{S}(t) = \frac{\text{Number of individuals with } T \geq t}{\text{Total sample size}}$$

i.e. total alive at time t divided by total number in the study. However, if censoring is present, then we can use Kaplan-Meier estimator

$$\hat{S}(t) = \Pi_{j:\, \tau j < t} \frac{r_j - d_j}{r_j}$$

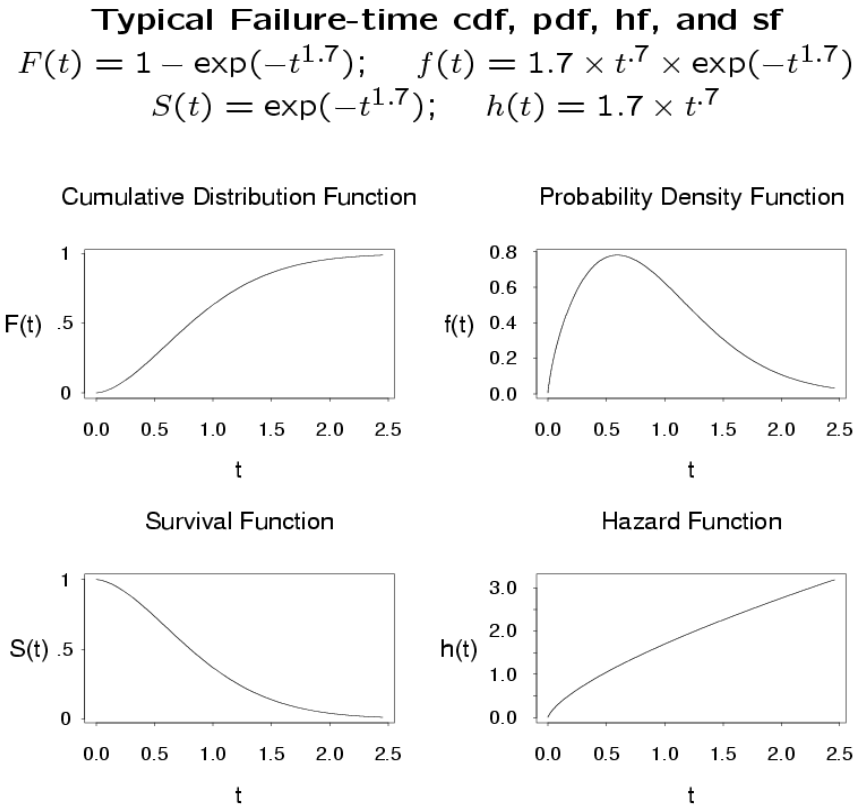
$$= \Pi_{j:\, \tau j < t} \left(1 - \frac{d_j}{r_j}\right),$$

where

- $\tau_1, \ldots \tau_k$ is the set of K distinct death times observed in the sample
- d_j is the number of deaths at τ_j
- r_j is the number of individuals "at risk" right before the j^{th} death time (everyone dead or censored at or after that time).

– c_j is the number of censored observations between the j^{th} and $(j + 1)^{st}$ death times. Censorings tied at τ_j are included in c_j.

A possible set of probability density, failure, survival, and hazard functions:



2.1 CONCEPTS OF COMPETING RISK ANALYSIS

2.1.1 Definition

The competing risk situation can actually be defined in a number of different ways As said earlier the competing risks situation arises when an individual can experience more than one type of event and the occurrence of one type of event hinders the occurrence of other types of events (Pintilie, 2006). Gooley *et al.* (1999) defined the concept of competing risk as the situation where one type of event "either precludes the occurrence of another event under investigation or fundamentally alters the probability of occurrence of this other event". The researcher and the statistician are more faced with the real life situation of competing events than single events happening. A competing risk event removes an individual from being at risk from an

outcome under consideration. For instance, when examining cancer incidence, cardiovascular disease is a competing risk because those who die of it are no longer at risk of cancer. This is a competing risk situation because death from the cardiovascular disease hinders the occurrence of cancer. So cancer is considered the event of interest, while death from the cardiovascular disease is considered a competing risk.

In the presence of competing risk, one should apply the usual survival methods with caution and one has to be aware of the consequences of their use (Pintilie, 2006). Treating the events of the competing causes as censored observations will lead to a bias in the Kaplan-Meier estimate if one of the fundamental assumptions underlying the Kaplan-Meier estimator is violated: the assumption of independence of the time to event of interest and the censoring distributions (H. Putter, M. Fiocco and R.B. Geskus, 2006). The censoring distributions here refer to the distribution of the time to the competing events. If the distributions of the time to the competing events were to be independent of the distribution to the time of the event of interest then the hazard at each time point would be same for those that have not experienced the event of interest and those that experienced a competing event. Clearly the hazards will not be the same for the two categories because an individual that has died from a competing risk will certainly not experience the event of interest (this makes the hazards different). When competing risks are present, Kaplan-Meier estimates cannot be interpreted as the true probabilities of survival (Pintilie, 2006). In this situation the Kaplan-Meier would overestimate the probability of failure and hence underestimate the corresponding survival probability. Kalbfleisch and Prentice, 1980 suggested an approach based on cumulative incidence function (CIF)[12]. This technique involves partitioning the probability of any event happening into separate probabilities for each type of event. For example in this present study, the events of interest as mentioned earlier are 'Re-operation', 'PVR B or C' and 'Reamotio'. We can estimate the probability of any of the three types of event occurring using the Kaplan-Meier method (1 – KM). The probability of *one* type of event is estimated using the CIF and at any particular point in time the sum of the cumulative incidence for each type of event is equal to the 1 – KM, which is calculated for all events.

[12] The CIF is the cumulative density function for each event type i (i = 1, 2, 3, …, y). More information in section (2.1.3)

2.1.2 Competing risks as a random variable

The event time and censoring mechanism can likewise be extended to the competing risk situation. Ideally we actually observe the minimum time of all events of interest. Suppose we have event times T_1,T_2,T_3, then the our time variable of interest is given by

$X = \min(T_1,T_2,T_3)$ and the censoring indicator, δ is given by

$$\delta = \begin{cases} 1, \text{ if } X = T_1 \text{ (PVR B or C in this analysis)} \\ 2, \text{ if } X = T_2 \text{ (Reamotio (re-detachment)} \\ 3, \text{ if } X = T_3 \text{ (Reoperation) and} \\ 0, \text{ if none of the three events occurred.} \end{cases}$$

2.1.3 Fundamental concepts

According to Pintilie (2006), some fundamental concepts in competing risk analysis are subdensity, subdistribution, subsurvivor, subhazard, cause-specific hazard and the hazard of the distribution. The cumulative incidence function and subdistribution are synonymous.

The subdensity function is simply the probability density function for each type of event, i. Mathematically, the subdensity if the derivative of the subdistribution:

$$f_i(t) = \frac{\partial F_i(t)}{\partial t}.$$

The CIF, or subdistribution, for an event of type i (where i = 1, 2, 3, …,y) is defined as the joint probability

$F_i(t) = P(T \leq t, C = i)$.

In other words, the CIF is the probability that an event of type i occurs at or before time t.

If no censoring, an empirical estimate of the CIF for the event of type i can be obtained as

$$\hat{F}_i(t) = \frac{Number\ of\ observations\ with\ T \leq t\ and\ C = i}{Total\ number\ of\ observations}.$$

If there is censoring (occurs when some patients did not experience any of the *y* events types) then the CIF estimator is given by

$$\hat{F}_i(t) = \sum_{\text{all j. } t_j \le t} \frac{d_{ij}}{n_j} \hat{S}(t_{j-1}),$$

where

d_{ij} is the number of events of type i at time t_j (number of failures at t_j)

n_j is the number of patients at risk at time t_j (the number free of any event at t_j)

$\hat{S}(t_{j-1})$ is the KM estimator of the probability of being free of any event just before time t_j.

The CIF estimator for an event of type i depends on the number of patients who have experienced type i event and also on the number who have not experienced any other type of event. The CIF represents the probability that an individual will experience an event of type i by time t (Pintilie, 2006).

The subhazard has the same interpretation as the hazard described in the survival analysis with one event only and summing all subhazards gives the overall hazard of any event type. Mathematically, the subhazard is given as

$$\tilde{h}_i(t) = \lim_{\partial t \to 0} \left[\frac{P(t < T \le t + \partial t, C = i \mid T > t)}{\partial t} \right],$$

which when simplified gives $\frac{f_i(t)}{S(t)}$.

The subsurvivor function involves fitting survivor function for each event type i. It is the probability that an event of type i does not occur by time t and is defined as the probability that an event of type i does not occur by time t:

$S_i(t) = P(T > t, C = i)$.

The cause-specific hazard is the hazard of the marginal survivor distribution. It is the hazard associated with a particular failure type or competing risk. Mathematically given by

$$h_i(t) = \frac{f_i(t)}{S_i(t)}.$$

2.1.4 Testing a two-level categorical covariate in the presence of competing risk

Often we either compare the cumulative incidence functions (or its hazard) and the cause-specific hazard depending on the aim of the analysis. This is because they both may not behave the same way and so the question of what to do becomes very important. Pintilie (2006) claimed, "In the absence of competing risks the survivor function is a monotonic function of the hazard; in the presence of competing

risks this property does not hold". For example, Gray (1988) showed that there are situations when the cause-specific hazard is larger in one group than in the other group but we may observe that their cumulative incidence functions may cross each other at some time point(s), thereby indicating equality at such point(s).

"When competing risks are present, two types of analysis can be performed: modelling the cause specific hazard and modelling the hazard of the subdistribution. When modelling the cause specific hazard, one performs the analysis under the assumption that the competing risks do not exist. This could be beneficial when, for example, the main interest is whether the treatment works in general. In modelling the hazard of the subdistribution, one incorporates the competing risks in the analysis. This analysis compares the observed incidence of the event of interest between groups. The latter analysis is specific to the structure of the observed data and it can be generalized only to another population with similar competing risks" (Putten et al, 2006)

The comparison of the cause-specific hazards[13] is made as if the other types of events did not exist; it is a good way of analyzing the data when one wants to find the biological mechanism underlying the specific outcome (Pintilie, 2006). Comparison of the cumulative incidence functions takes the competing events into account and doesn't assume that the failure times of the risks are independent of one another. It is usually a good practice to compare the CIFs or cause-specific hazard for the event of interests and as well for the competing risks. This is because the CIF for the event of interest may be low just because the risk of a competing event is high (Pintilie, 2006). The log-rank test, Gray's test and Pepe and Mori's test described next are very useful in the analysis of competing risk.

2.1.4.1 The Log-rank test

The log-rank test (a non-parametric method to test whether two or more survivor functions are equal) can be used to compare the cause-specific hazard of the groups of the covariate. The test statistic is given by

$$\frac{V_L^2}{\hat{Var}(V_L)} \sim \chi^2_{(1)}$$ (Follows a chi-square distribution with 1 degree of freedom),

[13] The cause-specific hazard can also be said to be the hazard of failing from a given cause in the presence of the competing events (Putten et al, 2006)

where $V_L^2 = \left[\sum_{j=1}^{r} \left(d_{1j} - n_{1j} \frac{d_j}{n_j} \right) \right]^2$ and

$$\hat{Var}(V_L) = \sum_{j=1}^{r} \frac{n_{1j} n_{2j} d_j (n_j - d_j)}{n_j^2 (n_j - 1)}.$$

In SAS 9.1, the test is done using 'proc lifetest' and in R, 'survdiff' function is used. The hypothesis of equality of survivor functions is rejected if the p-value of the log-rank test is less than the significance level (0.05 in this research). This test ignores the competing risk events. For comparison of the CIFs or its hazard taking the competing risk(s) into account, the Gray's test or the test introduced by Pepe and Mori (1993) can be used:

2.1.4.2 Gray's test

Gray's test compares the hazard of the CIF's (of the event of interest or the competing risk events) for the groups of the covariate under investigation. According to Pintilie (2006), the k-sample test introduced by Gray (1998) compares the weighted averages of the hazard of the subdistribution functions for the event of interest. The formula is given by

$$z_i = \int_0^T W_i(t)\left[h_i(t) - h_0(t)\right]\partial t,$$

where z_i is the score for group i of the covariate under investigation. T is the maximum time observed in both groups. W_i (t) is a weight function of the form $W_i = X(t)Q_i(t)$ for some function X(t) and

$$Q_i(t) = n_i(t)\frac{1 - \hat{F}_i(t-)}{\hat{S}_i(t-)},$$

$n_i(t)$ is number of individuals at risk at time t in group i,

$\hat{F}_i(t-)$ is the left-hand limit of the CIF for the event of interest in group i and

$\hat{S}(t-)$ is the left-hand limit of the survival probability (of being free of any event, estimated by the Kaplan-Meier method. $Q_i(t)$ represents an adjusted number of individuals at risk. (Pintilie, 2006).

2.1.4.3 Pepe and Mori's test

This method compares directly the CIF's. For covariate with only two levels, Pepe (1991) proved that

$$z = \sqrt{\frac{N_1 N_2}{N_1 + N_2}} \int_0^T W(t)\left[\hat{F}_1(t) - \hat{F}_2(t)\right] \partial t$$

is asymptotically normal with mean 0 and standard deviation σ. F_1 is the CIF for the event of interest for group 1 and F_2 for group 2. N_1 represents total number of subjects in group 1 and N_2 for group 2. Pintilie (2006) claims that Luna(1998) extended this test to k groups and the general form is

$$z_i = \sqrt{n_i} \int W(t)\left[\hat{F}_i(t) - \hat{F}_0(t)\right] \partial t$$

W(t) is a weight function,

F_i is the cumulative incidence in group i and

F_0 is the overall cumulative incidence for all groups.

The Gray's test can be easily implemented in R. For this reason the competing risk analysis carried out was based on the Gray's test

CHAPTER 3

3.0 METHODOLOGY

The methods used and procedures followed in carrying out the analysis are spelt out in this chapter. Firstly, the data was explored to see if we could gain insight into what we may be expecting from the later analysis. Next we derived the times of events and censoring. Using the time variable created, we estimated survivor functions for each event of interest. The cause-specific hazard of each endpoint was compared by the two arms of the surgical methods. Also the derived times of first event were used to estimate the CIFs and lastly, we tested some covariates for differences between the survivor functions of the categories of the covariate. All analysis was done separately for each subtrial (the phakic arm and the aphakic)

3.1.1 Exploratory data analysis

The proportion of patients with phakic and aphakic eye, the percentage of patients, the number of reoperations, the 'PVR B or C' incidence and the state of Reamotioness in each of the two treatment arms, Scleral Buckling and Primary Vitrectomy, was investigated. The total number of patients in each treatment arm was also investigated. A patient's record with PatNr 602007 was deleted because he had not visit day recorded for him. This left us with a remaining total of 680 patients in the study.

3.1.2 Time of events and censoring

Deriving the times to the occurrence of each of the three events and the censoring time was done using various data management steps in SAS 9.1. The codes used can be found in the appendix. A patient that had no event was given the time of the last known visit.

3.1.3 Survivor distribution of each event of interest

The survivor functions using each of the endpoints were estimated using the Kaplan-Meier method. This was done to show the behaviour of each event in the treatment arms. The Lifetest Procedure in SAS 9.1 was used for this and the codes can

be found in the appendix. The log-rank test was used to test the hypothesis of equality of the survivor functions.

3.1.4 Time of first event and censoring

Also, the times of the first occurring event of interest and the event type were derived using SAS 9.1. The codes used are in the appendix. A patient that didn't experience any of the three events was considered censored and giving the time of the last know visit. If the first occurring event is PVR BorC, its given event type 1. 2 if Reamotioness comes first and event type 3 if Reoperation comes first. If none of the three events was observed, then the patient is given event type 0 (censored).

3.1.5 Comparing cause-specific hazards

Firstly, the variables indicating the marginal distributions of the events of interest were derived. The variable equals 1 when the event of interest is the first event and 0 otherwise. A Kaplan-Meier analysis using the variable of times to first event, the corresponding indicator variable (indicating the marginal distribution of an event type i) as the censoring variable and the covariate (grouping variable) gave us the result of the comparison of cause-specific hazards. The p-value of the Log-Rank test from the lifetest procedure in SAS 9.1 tested the hypothesis of equality of the two cause-specific hazards compared. All the codes used are in the appendix.

3.1.6 Estimating the cumulative incidence functions (CIF's)

The three CIF's for the three events were estimated using the function 'cuminc' in R package. The cuminc function is found in the cmprsk (competing risk) library in R. The procedure also estimated the variances of the CIF's and graphical plots of the CIF's were also made. The estimation here was first done using 'PVR BorC' as event of interest and Reoperation as competing. Secondly, 'Reamotiones' as event of interest and Re-operation as the only competing risk. The codes used are all in the appendix.

3.1.7 Testing a two-level categorical covariate

The covariates 'OP' (operation type), was tested using the Log-rank test and Gray's test (R package was used here). The Log-rank test was used to compare the cause-specific hazards (hazard of the marginal distribution of the event of interest

'PVR B or C') in each group of the covariate. This test ignored the competing risks. On the other hand the Gray's method compared the hazard of the subdistribution of the event of interest in the presence of the competing risk and as well tested the equality of the hazard of the subdistribution of the competing risk in the groups of the covariate.

CHAPTER 4

4.0 RESULTS AND INTERPRETATIONS

The results are displayed following the procedure introduced in chapter 3.

4.1 Exploratory data analysis

Table 1.0 below shows the number of patients, incidences of re-operation, post-operative proliferative vitreoretinopathy (PVR) and retinal detachments for both scleral buckling and primary vitrectomy surgical methods in each of the two subtrials.

Table 4.0: summary statistics

	APHAKIC				PHAKIC		
	Primary vitrectomy	**Scleral buckling**	**TOTAL**		**Primary vitrectomy**	**Scleral buckling**	**TOTAL**
Patient	132 (49.81%)	133 (50.19%)	265 (38.97%)	**Patient**	206 (49.65%)	209 (50.36%)	415 (61.03%)
Reoperation	44 (40.37%)	65 (59.63%)	109 (41.13%	**Reoperation**	135 (61.64%)	84 (38.36%)	219 (52.17%)
PVR	20 (40%)	30 (60%)	50 (18.87%)	**PVR**	34 (56.67%)	26 (43.33%)	60 (14.46%)
Retinal detachment	28 (34.57%	53 (65.43%	81 (30.57%)	**Retinal detachment**	52 (48.60%	55 (51.40%)	107 (25.73%)

A total of 50 patients in the aphakic subtrial (18.87%) experienced a post-operative PVR BorC incidence but a lesser percentage of patient (14.46%) in the phakic group experienced a PVR BorC. Also, there was a higher percentage of patients that experienced a post-operative incidence of retinal detachment in the aphakic group (30.57%) than the percentage of 25.73% in the phakic group. However, the phakic group has a higher incidence of reoperations (52.17%) than the 41.13% percent of patients that experienced reoperation in the aphakic subtrial.

In summary, the PVR incidence (18.87%) and the incidence of retinal detachment (30.57%) were higher for aphakic patients but the phakic patients had a higher reoperation incidence (52.17%).

4.2 Kaplan-Meier estimate of the time to occurrence of Proliferative Vitreoretinopathy Stage B or C (PVR_BorC)

Analysis done by subtrial for the two surgical methods: Scleral buckling and Primary Vitrectomy.

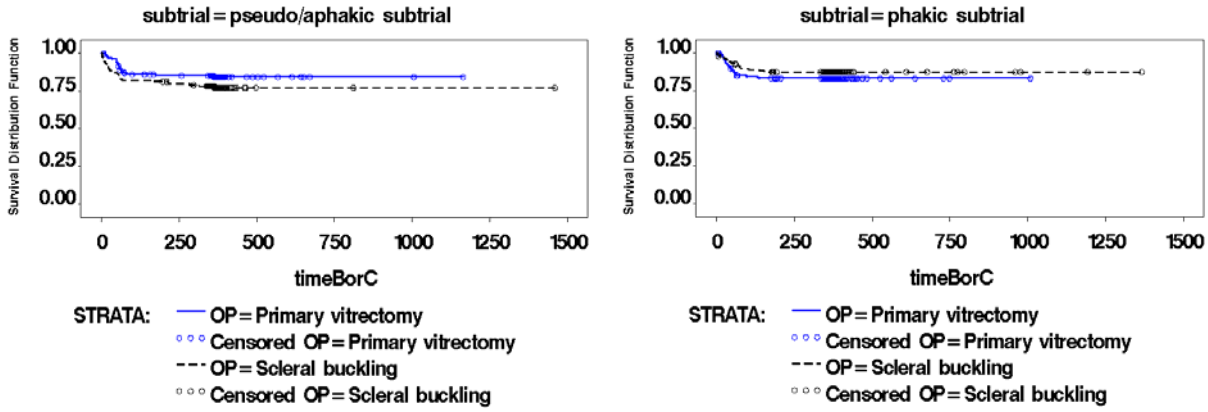


Fig. 4.0 a and b: survival experience of the post-operative incidence of proliferative vitreoretinopathy

Table 4.1a: Aphakic subtrial

Stratum	OP	Total	Failed	Censored	Percent Censored	Mean surv.time, stand.error	Chi-sq. of Log-Rank test, pvalue
1	Primary vitrectomy	132	20	112	84.85	316.65, 9.92	2.325, 0.1273
2	Scleral buckling	133	30	103	77.44	298.45, 11.49	

Table 4.1b: Phakic subtrial

Stratum	OP	Total	Failed	Censored	Percent Censored	Mean surv.time, stand.error	Chi-sq. of Log-Rank test, pvalue
1	Primary vitrectomy	206	34	172	83.50	120.82, 2.56	1.5174, 0.2180
2	Scleral buckling	209	26	183	87.56	141.75, 2.53	

Discussion:

More than 50% of the patients in both subtrials survived (did not experience the a PVR B or C) till end of the study so it wasn't possible to calculate the median survival time. The percentage of censoring was very high for both treatment arms of both subtrials (table 4.1). The mean survival time was higher for the vitrectomy group

of the aphakic patients (table 4.1). In the phakic category, the scleral buckling group had the higher mean survival time. The p-valued of the Log-Rank test indicated that there was no significant difference in the survival experiences (occurrence of PVR B or C) of the patients treated by scleral buckling and primary vitrectomy surgical methods in both the aphakic and phakic subtrials separately.

4.3 Kaplan-Meier estimate of the time to occurrence of first retinal re-detachment (reamotiones)

Analysis was done by subtrial for the two surgical methods: Scleral buckling and Primary Vitrectomy.

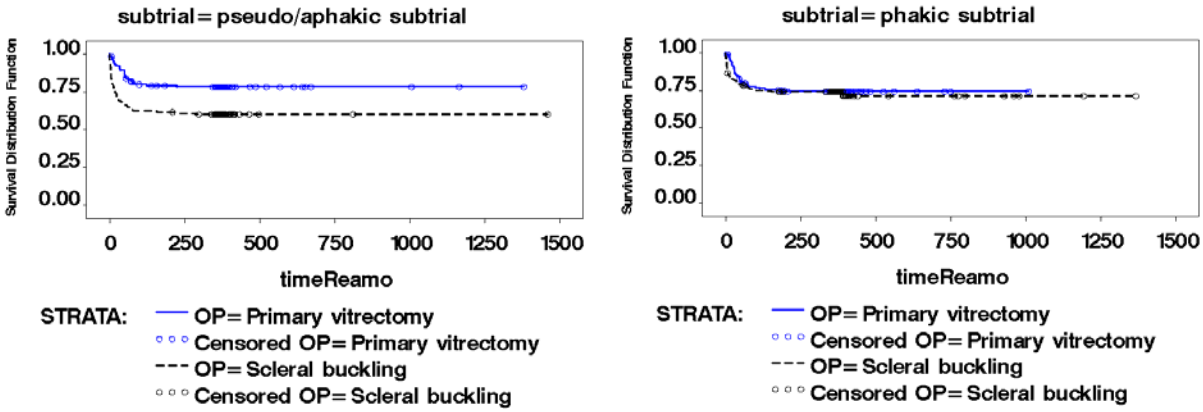


Fig. 4.1 a and b: survival experience of the post-operative incidence of retinal detachment

Table 4.2a: Aphakic subtrial

Stratum	OP	Total	Failed	Censored	Percent Censored	Mean surv.time, stand.error	Chi-sq. of Log-Rank test, pvalue
1	Primary vitrectomy	132	28	104	78.79	185.79, 2.56	12.3069, 0.0005
2	Scleral buckling	133	53	80	60.15	183.22, 2.53	

Table 4.2b: Phakic subtrial

Stratum	OP	Total	Failed	Censored	Percent Censored	Mean surv.time, stand.error	Chi-sq. of Log-Rank test, pvalue
1	Primary vitrectomy	206	34	172	83.50	185.79, 2.56	0.2699, 0.6034
2	Scleral buckling	209	26	183	87.56	183.22, 2.53	

Discussion

Also the survival curves in both subtrials did not descend low enough to get to the survival probability of 0.5 thus the median survival time could not be estimated. There is a much wider separation between the two curves in the aphakic subtrial right from the 0 time to the end of study than seen in the phakic subtrial. The p-value (<0.05) of the Log-Rank test confirmed the significance of the Chi-Square value, and that meant that treatment with vitrectomy was more effective against the incidence of retinal re-detachment than treatment with the scleral buckling surgical method for patients with the aphakic eye condition. There was no significant difference between the occurrences of retinal re-detachment between the two treatment groups of patients in the phakic case (insignificant p-value of 0.6034).

4.4 Kaplan-Meier estimate of the time to occurrence of first re-operation for the two surgical methods.

Analysis was done by subtrial for Scleral buckling and Primary Vitrectomy.

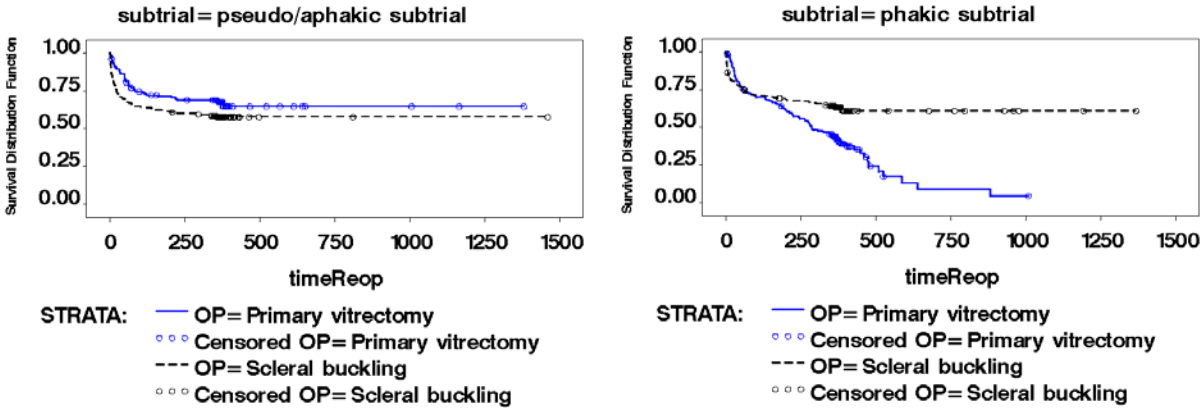


Fig. 4.2 a and b: survival experience of the incidence of reoperation

Table 4.3a: Aphakic subtrial

Stratum	OP	Total	Failed	Censored	Percent Censored	Mean surv.time, stand.error	Chi-sq. of Log-Rank test, pvalue
1	Primary vitrectomy	132	42	90	68.18	279.10, 13.39	3.7988, 0.0513
2	Scleral buckling	133	56	77	57.89	228.42, 13.99	

Table 4.3b: Phakic subtrial

Stratum	OP	Total	Failed	Censored	Percent Censored	Mean surv.time, stand.error	Chi-sq. of Log-Rank test, pvalue
1	Primary vitrectomy	206	129	77	37.38	324.20, 25.48	16.2905, 0.0001
2	Scleral buckling	209	76	133	63.64	270.30, 11.40	

Discussion

For the aphakic subtrial, the p-value of the Log-Rank test is not significant. We therefore do not have sufficient evidence to say that either of the two surgical methods is better than the other. The chances of not experiencing the incidence of reoperation are not significantly different between the two methods. However, for the phakic subtrial, the p-value (<0.05) of the Log-rank test confirms that the scleral buckling surgical method gave the patients comparatively higher chance of survival (not experiencing the re-operation) and thus may be the preferred method for the phakic patients.

4.5 Estimating the cumulative incidence function (CIF)

4.5.1 Analysis for PVR as event of interest and reoperation as the only competing event.

Aphakic subtrial

The CIF estimates at any time points say 0, 250, 500, 750, 1000, 1250, 1500 days as computed by the cuminc function is given in table 4.3 (shown only for the purpose of clarity in this case only. It was not shown in latter cases).

Table 4.4: Aphakic subtrial, estimates and variances of the probability of PVR and Reoperation

Event	Time point (days), variance					
	250	500	750	1000	1250	1500
PVR_BorC	0.1486355, 0.0005605956	0.1655061, 0.0006331389	0.1655061, 0.0006331389	0.1655061, 0.0006331389	0.1655061, 0.0006331389	NA
Reop	0.1033164, 0.0004223459	0.1398228, 0.0008876980	0.1398228, 0.0008876980	0.1398228, 0.0008876980	0.1398228, 0.0008876980	NA

NA: not applicable

The graph of the CIFs of the two events is given in fig 4.3:

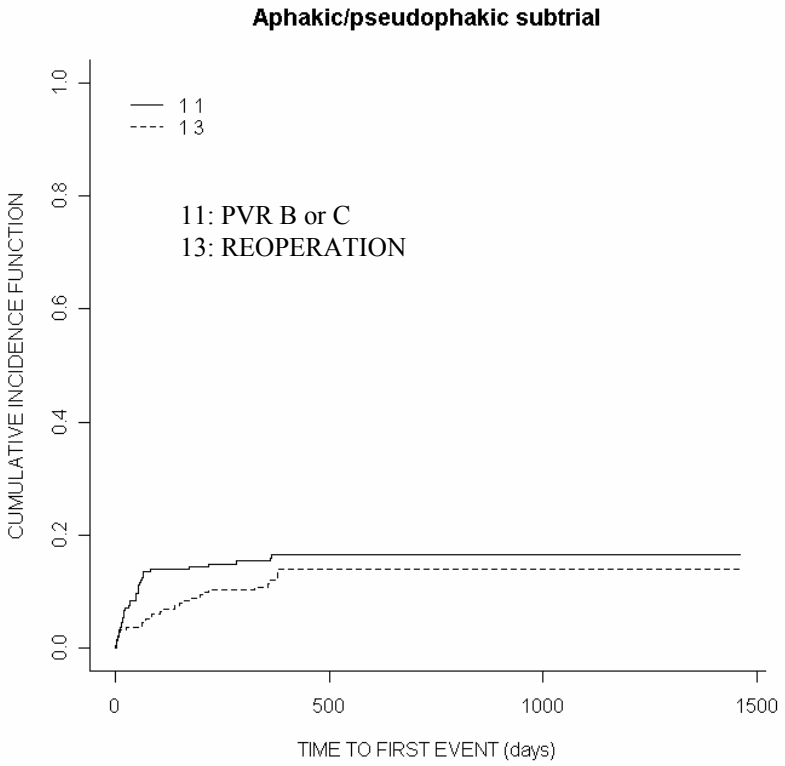


Fig. 4.3 Cumulative incidence for the PVR (main endpoint) and Reoperation (competing event)

For the aphakic subtrial, the CIF for PVR rises very sharply from 1 to about 100 days after treatment and afterwards rises slowly until about 400 days after which it remains constant till the study closed. That of re-operation rises gradually soon after treatment until about 400 days after which it also remained constant till the study ended.

The result of the Gray's test, which compared the each of the two CIFs above for differences between the two treatment arms, is shown in figures 4.4 and 4.5 below:

Gray's Tests:

	statistic	pv	df
PVR	1.0525281	0.3049256	1
Re-operation	0.1277623	0.7207635	1

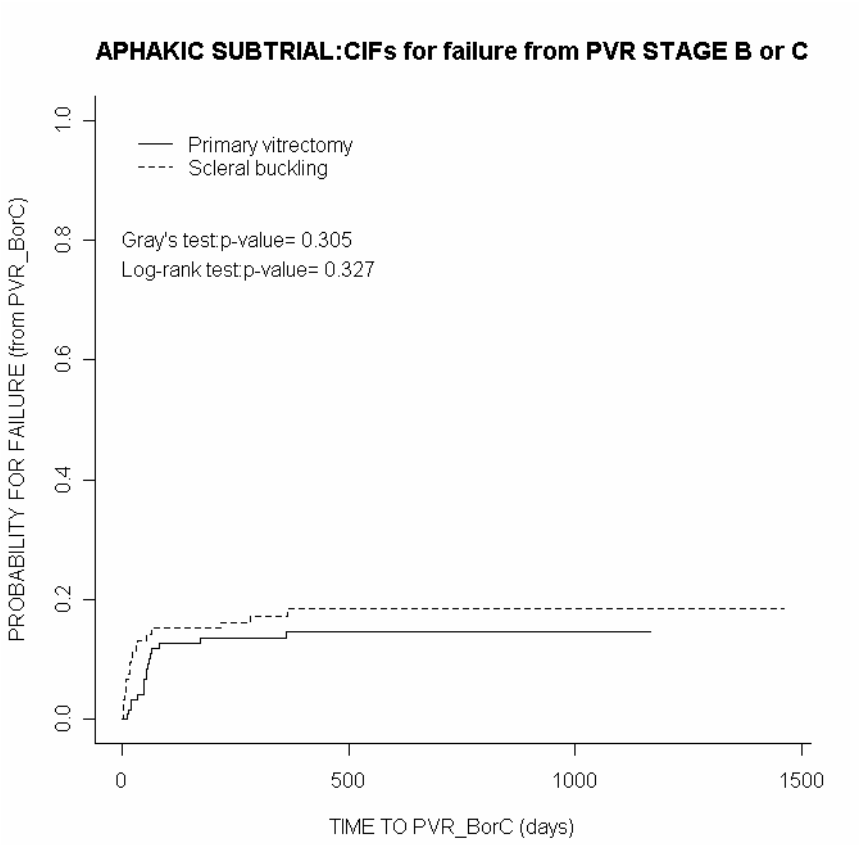


Fig. 4.4: Cumulative incidence function for failure from Post-operative Proliferative Vitreoretinopathy

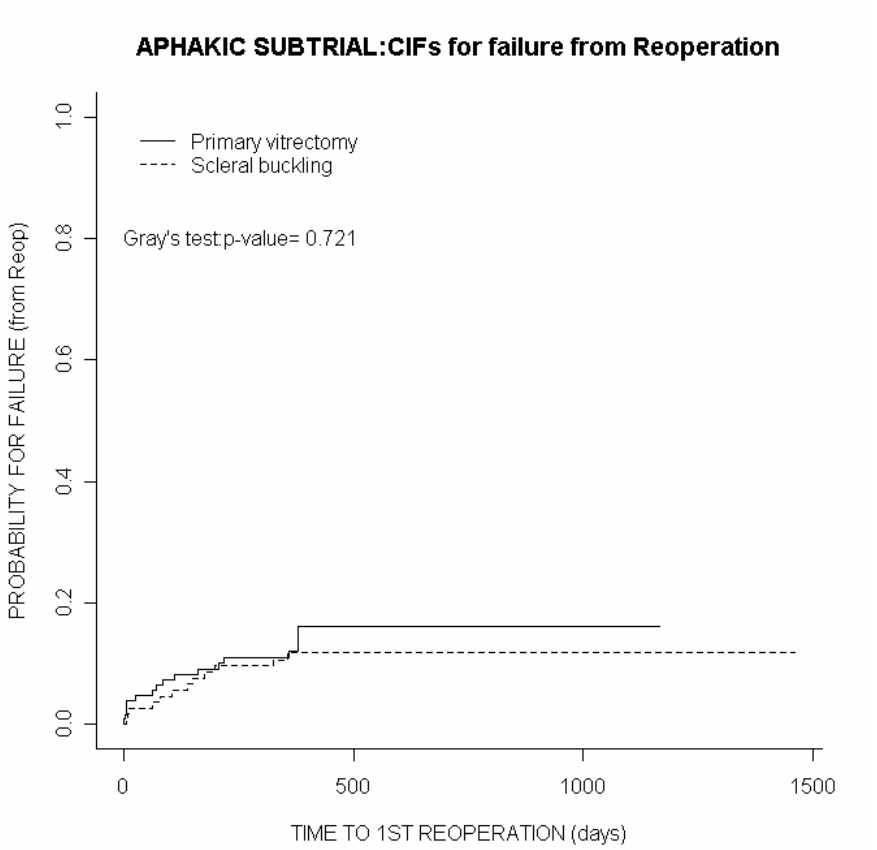


Fig. 4.5: comparing the CIF of the competing event between the two surgical methods

Discussion

Ignoring the competing risk, the Log-Rank test p-value of 0.327 shows that the hazard of experiencing the event of 'PVR BorC' is more or less the same for patients treated with either surgical method for the aphakic patients. In the presence of the competing risk of re-operation, the Gray's test p-value of 0.305 shows that there still is no difference between the two methods and the Gray's test p-value of 0.721 indicated that the competing risk are not different between the two treatment arms.

Phakic subtrial

The graph of the CIF for the two events is shown below:

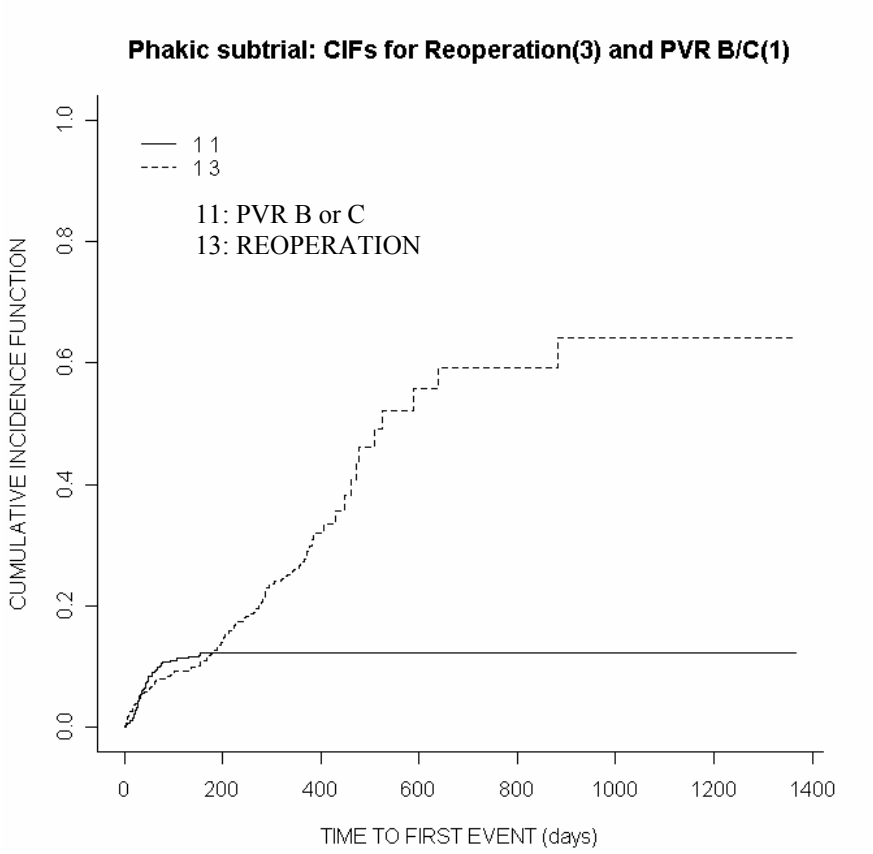


Fig. 4.6: Cumulative incidence for the PVR (main endpoint) and Reoperation (competing event)

The result of the Gray's test, which compared each of the two CIFs above for differences between the two treatment arms, is shown below in figures 4.7 and 4.8:

Gray's test

	statistic	pv	df
PVR	0.1755434	6.752315e-01	1
Reoperation	29.0260228	7.141252e-08	1

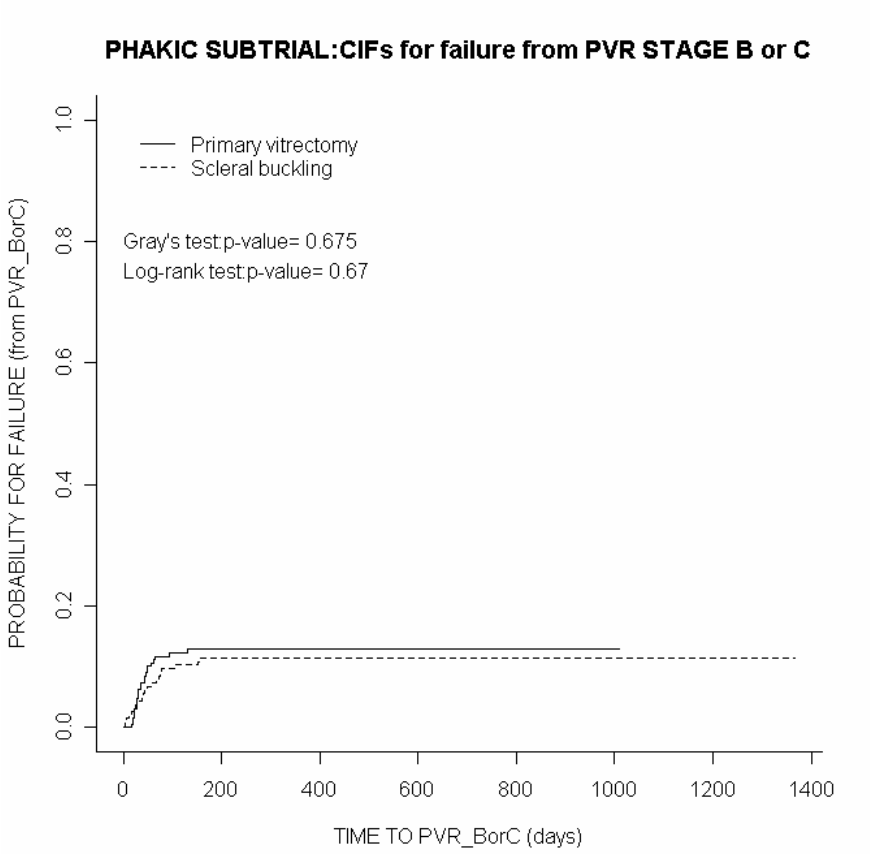


Fig. 4.7: Cumulative incidence function for failure from Post-operative Proliferative Vitreoretinopathy

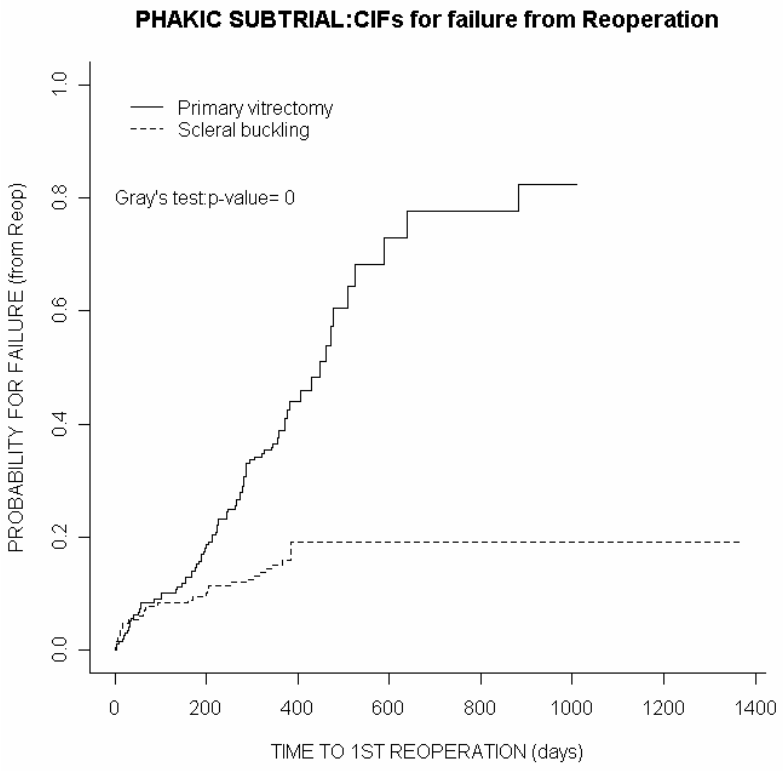


Fig. 4.8: comparing the CIF of the competing event between the two surgical methods

Discussion

Fig. 4.6 showed a very high incidence of re-operation rising to as high as 60%. The p-value of the Log-Rank test (0.67) showed that there is no significant difference in the incidence of PVR BorC between the surgical methods for the phakic patients while ignoring the competing risk. The Gray's test p-value of 0.675 showed that there is no difference in the incidence of PVR BorC between the two treatment groups in the presence of reoperation, the supposed competing risk. Yet the Gray's test p-value of 0 showed that the competing risk, reoperation is very significantly different between the two surgical methods.

4.5.2 Analysis for retinal re-detachment as event of interest and re-operation as the only competing event.

Aphakic subtrial

The graph of the CIF for the two events is shown in fig. 4.9 below:

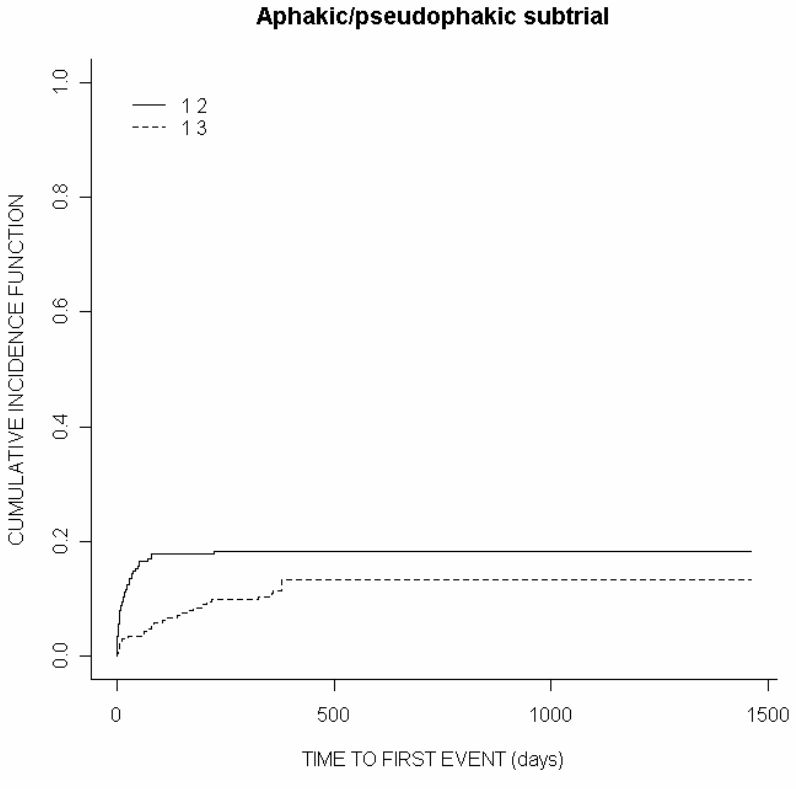


Fig. 4.9: Cumulative incidence for retinal re-detachment (main endpoint) and Reoperation (competing event)

The result of the Gray's test, which compared each of the two CIFs above for differences between the two treatment arms, is shown in figures 4.10 and 4.11 below:

Gray's test

	statistic	pv	df
Re-detachment	7.9592318	0.004784272	1
Reoperation	0.4298569	0.512059182	1

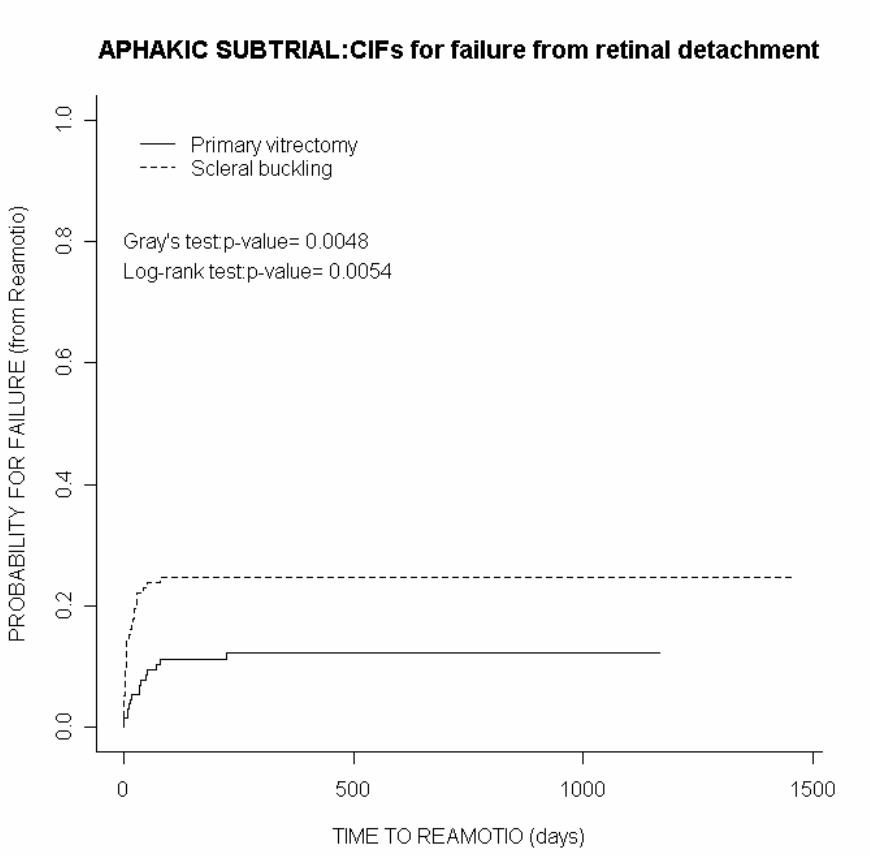


Fig. 4.10: Cumulative incidence function for failure from retinal re-detachment

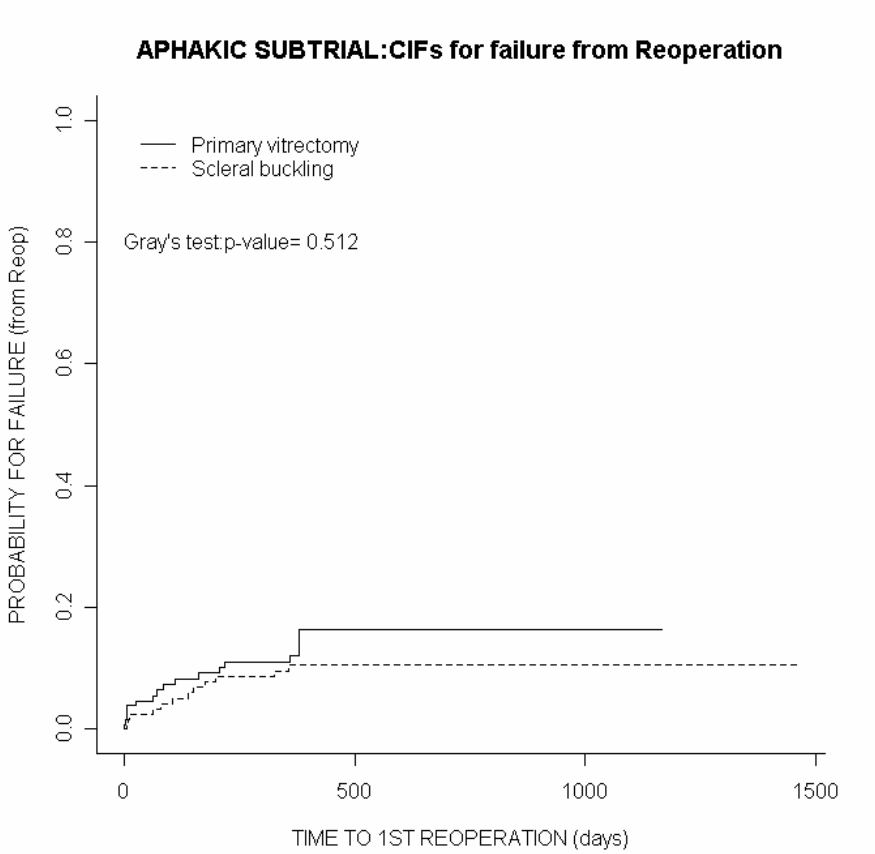


Fig. 4.11: comparing the CIF of the competing event between the two surgical methods

Discussion

The incidence of retinal detachment differs significantly between the surgical methods for the aphakic patients (Log-Rank test p-value = 0.0054) in the absence of the competing risk and as well in the presence of the competing risk (Gray's test p-value = 0.0048). Patients in the two treatment groups have the same level of risk of the competing event of reoperation (Gray's test p-value comparing the CIFs of reoperation between the two treatment = 0.512).

Phakic subtrial

The graph of the CIF for the two events is shown in fig. 4.12 below:

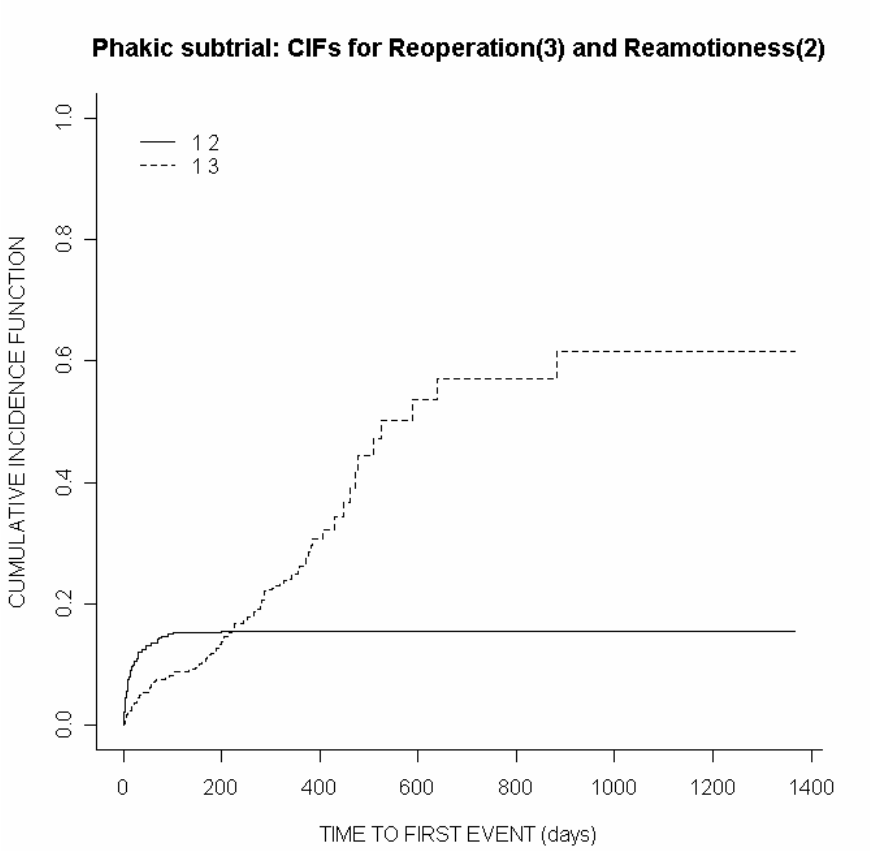


Fig. 4.12: Cumulative incidence for retinal re-detachment (main endpoint) and Reoperation (competing event)

The result of the Gray's test, which compared each of the two CIFs above for differences between the two treatment arms, is shown in figures 4.13 and 4.14 below:

Gray's test

	stat	pv	df
Retinal re-detachment	3.047891	8.084208e-02	1
Reoperation	34.626891	3.993514e-09	1

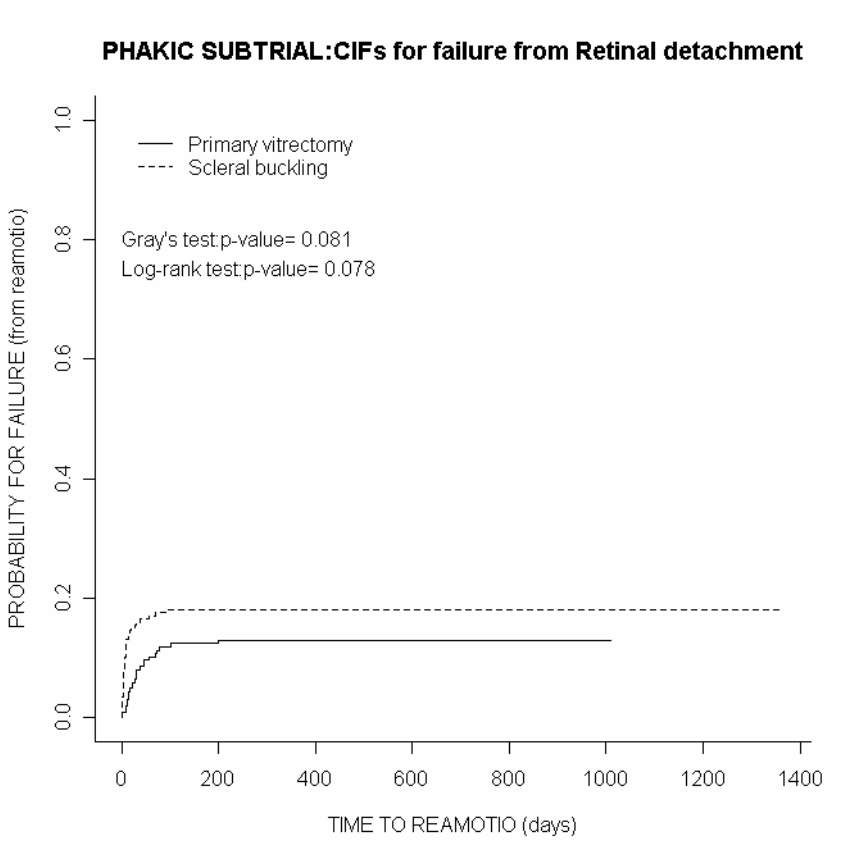


Fig. 4.13: Cumulative incidence function for failure from retinal re-detachment

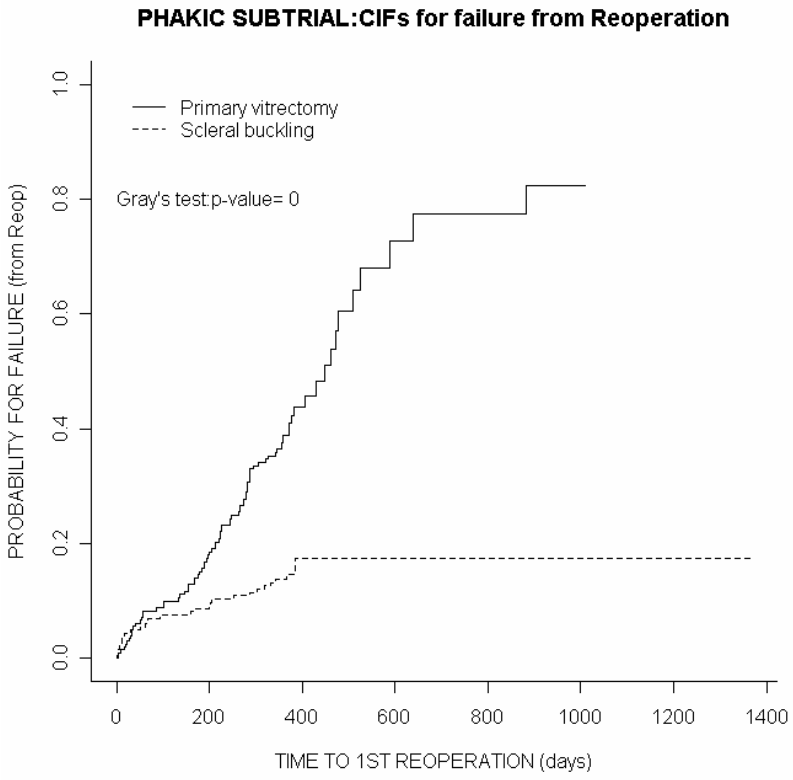


Fig. 4.14: comparing the CIF of the competing event between the two surgical methods

Discussion

For the phakic subtrial, there was no significant difference in the risk of retinal detachment between the two treatment methods while ignoring the competing risk of re-operation (Log-Rank test p-value = 0.078). There still was no significant difference in the incidence of retinal detachment between the two methods in the presence of the competing risk (Gray test p-value = 0.081). However, the patients treated with primary vitrectomy experienced significantly different (higher) competing risk of re-operation (Gray test p-value = 0).

4.5.3 Summary of result

The tables 4.5 and 4.6 highlight the p-values for the log-rank and the Gray's test. from the competing risk analysis.

Table 4.5: Log-rank and Gray's test result when PVR B or C was taken as event of interest and re-operation as the competing event.

EVENTS / COMPETING RISK	APHAKIC		PHAKIC	
	Test	P-value	Test	P-value
PVR B or C	Log-rank	0.327	Log-rank	0.67
	Gray's	0.305	Gray's	0.675
Reoperation (competing)	Gray's	0.721	Gray's	0

Table 4.6: Log-rank and Gray's test result when Retina re-detachment (reamotio) was taken as event of interest and re-operation as the competing event.

EVENTS / COMPETING RISK	APHAKIC		PHAKIC	
	Test	P-value	Test	P-value
Re-detachment	Log-rank	0.0054	Log-rank	0.078
	Gray's	0.0048	Gray's	0.081
Reoperation (competing)	Gray's	0.512	Gray's	0

CHAPTER 5

5.0 DEDUCTIONS FROM RESULTS, AND CONCLUSIONS

5.0.1 When PVR B or C was event of interest

For the aphakic subtrial, there was no sizeable difference between surgery with primary vitrectomy and that with scleral buckling as regards the postoperative incidence of proliferative vitreoretinopathy (PVR B or C) both in the absence and presence of the competing risk of re-operation. The two groups of patients are exposed to the same risk of re-operation and as well have the same risk of experiencing a PVR B or C after surgery.

For the phakic subtrial, the risk of re-operation is much higher for the patients treated with primary vitrectomy than the patients treated with scleral buckling. We do not have a sizeable difference between the risk of PVR B or C between patients treated with primary vitrectomy and those with scleral buckling.

The risk of PVR is the same for both surgical methods in aphakic as well as the phakic patients.

5.0.2 When retinal detachment is event of interest

For the aphakic subtrial, the risk of post retinal detachment is higher for the patients treated with scleral buckling method than with primary vitrectomy both in the absence and in the presence of the competing risk of re-operation. Patients treated with either method experienced the same risk of re-operation.

For the phakic subtrial, the risk of re-operation is much higher for patients with primary vitrectomy than those treated with scleral buckling method but there is no difference between the patients treated with primary vitrectomy and scleral buckling method as regards the risk of retinal re-detachment.

5.0.3 Regular survival analysis and the competing risk analysis

The results from the competing risk analysis discussed were not much different from those from the one-event at a time survival analysis done in sections 4.2 to 4.4 where the time to occurrence of re-operation was significantly different

only for phakic patients (patients treated with scleral buckling had the higher chance of not experiencing a re-operation). Also the time to occurrence of retinal re-detachment was significantly different only for the aphakic patients (patients treated with primary vitrectomy had the higher chance of not experiencing a re-detachment). There was no sizeable difference between the two treatment groups in the chance of experiencing a 'PVR B or C' for both aphakic and phakic patients.

Although similar results or same deductions were made from the regular one-event analysis and the competing risk analysis done in this study, it has at least shown the competing nature of our events and observed re-operation not to create a difference in the occurrences of post operative 'PVR B or C' or retinal re-detachment between the two surgical methods in each subtrial.

5.1 CONCLUSIONS

The primary vitrectomy surgical method should be the better method for the aphakic patients because the aphakic patients treated with this method experienced a lower risk of retinal re-detachment than the phakic patients treated with scleral buckling.

Scleral buckling surgical method should be the preferred method for the phakic patient because of the higher risk of re-operation associated with the method of primary vitrectomy for patients of this subtrial.

LIMITATION OF THE STUDY

I wished I had more books on competing risk analysis at my disposal. Maybe I would have been able to do more than I did in this study.

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Gooley, T. A., Leisenring, W., Crowler, J. And Storer, B. E. (1999). Estimation of Failure Probabilities in the Presence of Competing Risks: New Representation of Old Estimators. *Statistics in Medicine,* **18**, 695-706.

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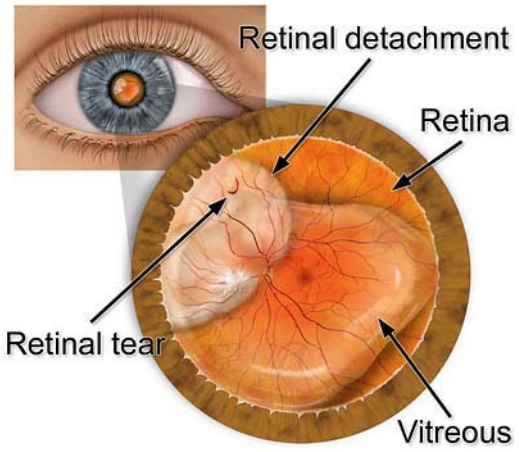
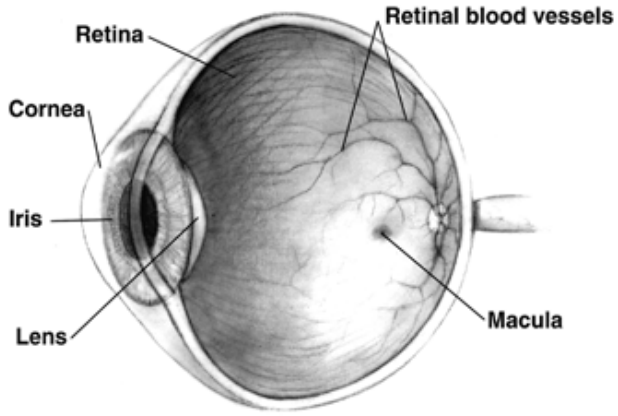
APPENDIX

A.0 RETINAL DETACHMENT



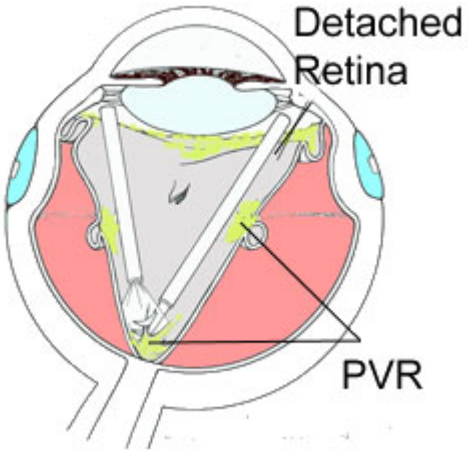
Source: http://www.eyemdlink.com/Condition.asp?ConditionID=383

Fig a.0 the interior parts of they human eye



Source: *http://en.wikipedia.org/wiki/Image:Human_eye_cross-sectional_view_grayscale.png*

Fig a.1 cross sectional view of the human eye



Source: http://www.retinatexas.com/vitreoretinopathy.html

Fig a.2 proliferative vitreoretinopathy with detached retina

A.1 SURGERY PROCEDURE

Scleral buckling:

- Usage of silicone sponges and / or silicone encircling bands or a combination of both according to the surgeon's choice.
- Coagulation using cryopexy
- Intraocular tamponade with injection of BSS, air or SF_6, if necessary.
- Drainage of subretinal fluids with a needle or using electrolysis, if necessary
- Puncture of the anterior chamber, if necessary.

Primary Vitrectomy

- Usage of an encircling band based on the surgeon's decision.
- Pars plana vitrectomy.
- Removal of the flap of the retinal tear, if necessary.
- Usage of PFCL, if necessary.
- Coagulation with cryopexy or laserkoagulation
- Intraocular tamponade with a 20-40% SF_6 /air mixture.
- Draining retinotomies, if necessary

A.2 SAS CODES USED

```
*calculating event time in days for patients who had PVR_BorC (i.e. the EVENT of
interest);
data thesis.spr_few2 ;set thesis.spr_few;eventtimeBorC=(PVRD - SurgD);run;

*calculating time in days for patients who did not have PVR_BorC (i.e. the censored
times);
data thesis.spr_few3 ;set thesis.spr_few3;days3=eventtimeBorC;
if eventtimeBorC=. then days3=(V4D - SurgD);run;

*deriving the censoring indicator for PVR_BorC;
data thesis.spr_few3 ;set thesis.spr_few3;censoring3=eventtimeBorC;
if eventtimeBorC=. then censoring3=1;else censoring3=0;run;

*calculating event time in days for patients who had ReAmotio (i.e. the 3rd EVENT of
interest);
data thesis.spr_few3 ;set thesis.spr_few3;eventtimeReAmo=(firstReAmotioD - SurgD);run;

*calculating time in days for patients who did not have ReAmotio (i.e. the censored
times);
data thesis.spr_few3 ;set thesis.spr_few3;days4=eventtimeReAmo;
if eventtimeReAmo=. then days4=(V4D - SurgD);run;

*deriving the censoring indicator for ReAmotio;
data thesis.spr_few3 ;set thesis.spr_few3;censoring4=eventtimeReAmo;
if eventtimeReAmo=. then censoring4=1;else censoring4=0;run;

*making a copy of thesis.spr_few3 in order to later reduce observations to no. of
patients in study;
data thesis.spr_few4;set thesis.spr_few3;run;

*deleting repeated observations in the dataset to have only the number of patients in
the study;
proc sort data=thesis.spr_few4 NODUPKEY;by PatNr;run;

*deleting data for Patient with PatNr 602007 (no visitday at all);
data thesis.spr_few4;set thesis.spr_few4; if v4d=. then delete;run;

*determining the patients with none of the three events (coded 0);
data thesis.spr_few5;set thesis.spr_few5;
if censoring = censoring3 = censoring4 = 1 then event = 0;run;

*deriving the eventtimeReop;
data thesis.spr_few5;set thesis.spr_few5;
eventtimeReop = days2;
if censoring = 1 then eventtimeReop = .;run;

*allocating the time of last visit to the patients that didn't experience any event ;
data thesis.spr_few5;set thesis.spr_few5;
if event = 0 then dayoffirstevent2 = (V4D - SurgD);run;

*calculating the first occuring event;
data thesis.spr_few9;set thesis.spr_few5;
firsteventtime=min(eventtimeBorC,eventtimeReAmo,eventtimeReop);run;

*allocating the time of a patient's last visit (v4d) to patients that didn't
experience any event;
data thesis.spr_few9;set thesis.spr_few9;firsteventtime2 = firsteventtime;
if firsteventtime = . then firsteventtime2=(v4d - surgd);run;

*determining which event occured first: SAME RESULT AS ABOVE;
data thesis.spr_few10;set thesis.spr_few10;
if eventtimeBorC = eventtimeReop = eventtimeReAmo = firsteventtime ne . then
firstevent2=1;
if eventtimeBorC = eventtimeReop = firsteventtime then firstevent2=1;
if eventtimeBorC = eventtimeReAmo = firsteventtime then firstevent2=1;
if eventtimeReAmo = eventtimeReop = firsteventtime then firstevent2=2;
if eventtimeReop = firsteventtime then firstevent2=3;
if eventtimeBorC = firsteventtime then firstevent2=1;
if eventtimeReAmo = firsteventtime then firstevent2=2;run;

data thesis.spr_few10;set thesis.spr_few10;
firstevent3=firstevent2;if event = 0 then firstevent3=0;run;

*SOLVING THE PROBLEM OF THREE EVENTS ON SAME DAY;
```

```
data thesis.spr_few10;set thesis.spr_few10;
if eventtimeBorC = eventtimeReop = eventtimeReAmo ne . then firstevent4=1;run;

*WHEN THREE EVENTS HAPPEN ON SAME DAY, TAKE PVRBorC as first event;
data thesis.spr_few10;set thesis.spr_few10;
firstevent5=firstevent3;if firstevent4=1 then firstevent5=1;run;

data thesis.spr_few11;set thesis.spr_few10;
keep PatNr op Subtrial surgeon catop nobreakps multiplebr largebr traction sex
maculamh reops reamotiones pvr_boderc days3 censoring3 days4 censoring4 days2
censoring firsteventtime2 firstevent5;run;

*preparing FINAL DATA to be used henceforth for all analysis;
data thesis.spr_few12;set thesis.spr_few11;
timeReop=days2; censReop=censoring; timeBorC=days3; censBorC=censoring3;
timeReamo=days4; censReamo=censoring4;
firsteventtime=firsteventtime2; firstevent=firstevent5;
drop firsteventtime2 firstevent5 days2 censoring days3 censoring3 days4
censoring4;run;

*FINAL DATA TO BE USED HENCEFORTH;
data thesis.spr_few13;set thesis.spr_few12;run;

proc sort data=thesis.spr_few13;by subtrial;run;
goptions reset=all ftext=swissb htext=2.0;
symbol1 l=1 c=blue v=star w=2;symbol2 l=3 c=black v=circle w=2;nolegend;
*Kaplan-Meier estimate for PVR_BorC event;
proc lifetest data=thesis.spr_few13 plots=(s) outsurv=PVR_BorC;
time timeBorC*censBorC(1);strata op;by subtrial;run;

goptions reset=all ftext=swissb htext=2.0;
symbol1 l=1 c=blue v=star w=2;symbol2 l=3 c=black v=circle w=2;
*Kaplan-Meier estimate for Reamotioness event;
proc lifetest data=thesis.spr_few13 plots=(s) outsurv=Reamotio;
time timeReamo*censReamo(1);strata op;by subtrial;run;

goptions reset=all ftext=swissb htext=2.0;
symbol1 l=1 c=blue v=star w=2;symbol2 l=3 c=black v=circle w=2;
*Kaplan-Meier estimate for firstreoperation event;
proc lifetest data=thesis.spr_few13 plots=(s) outsurv=firstReop;
time timeReop*censReop(1);strata op;by subtrial;run;

*creating the marginal distribution indicator of the event of interest(PVR_BorC);
data thesis.spr_few13;set thesis.spr_few13;
if firstevent = 1 then margPVR = 1; else margPVR = 0;run;

*comparing the cause specific hazard for the event of interest by treatment and
subtrial;
goptions reset=all ftext=swissb htext=2.0;
symbol1 l=1 c=blue v=star w=2;symbol2 l=3 c=black v=circle w=2;
proc lifetest data=thesis.spr_few13 plots=(s); *outsurv=firstReop;
time firsteventtime*margPVR(0);strata op;by subtrial;run;

*creating the marginal distribution indicator of Reamotio if we take it
as the event of interest;
data thesis.spr_few13;set thesis.spr_few13;
if firstevent = 2 then margReamo = 1; else margReamo = 0;run;

*comparing the cause specific hazard for Reamotio taken as the event of interest
by treatment and subtrial;
goptions reset=all ftext=swissb htext=2.0;
symbol1 l=1 c=blue v=star w=2;symbol2 l=3 c=black v=circle w=2;
proc lifetest data=thesis.spr_few13 plots=(s); *outsurv=firstReop;
time firsteventtime*margReamo(0);strata op;by subtrial;run;

*creating the marginal distribution indicator of Reoperation if we take it
as the event of interest;
data thesis.spr_few13;set thesis.spr_few13;
if firstevent = 3 then margReop = 1; else margReop = 0;run;

*comparing the cause specific hazard for Reamotio taken as the event of interest
by treatment and subtrial;
goptions reset=all ftext=swissb htext=2.0;
symbol1 l=1 c=blue v=star w=2;symbol2 l=3 c=black v=circle w=2;
proc lifetest data=thesis.spr_few13 plots=(s); *outsurv=firstReop;
time firsteventtime*margReop(0);strata op;by subtrial;run;

*creating the indicator variable if we assume 2events only:
event of interest as PVR_BorC AND Reoperation as competing risk.
```

```
Reamotio will now be taken as no event i.e. censored;
data thesis.spr_few13;set thesis.spr_few13;evtNoReamo = firstevent;
if firstevent = 2 then evtNoReamo = 0;run;

*creating the indicator variable if we assume 2events only:
event of interest as Reamotioness AND Reoperation as competing risk.
PVR_BorC will now be taken as no event i.e. censored;
data thesis.spr_few13;set thesis.spr_few13;evtNoPVR = firstevent;
if firstevent = 1 then evtNoPVR = 0;run;

*EXPLORATORY DATA ANALYSIS;
proc freq data=thesis.spr_few13;table sex*op Reops*op PVR_BoderC*op Reamotiones*op;
by subtrial;run;
```

A.3 R CODES USED

ANALYSIS FOR PVR AS EVENT OF INTEREST AND REOPERATION AS THE ONLY COMPETING EVENT OR AS THE ONLY OTHER EVENT

```
### Reading the dataset aphakicFinal.csv into R ###
aphak=read.table('D:/Dy/aphakicFinal.csv',sep=',',header=T)
aphak

### loading the competing risk package ###
library(cmprsk)

### comparing the cause-specific hazard of the marginal distribution of PVR_BorC by the
2 treatment groups ###
fit1=survdiff(Surv(aphak$firsteventtime,aphak$margPVR)~aphak$OP)
fit1
fit1$chisq
logRankTestPvalue=1-pchisq(fit1$chisq,1)
logRankTestPvalue

### calculating the CIF estimates for each type of event and the variance ###
fit3=cuminc(aphak$firsteventtime,aphak$evtNoReamo)
fit3

### obtaining the CIF estimates at any time points say 0,250,500,750,1000,1250,1500 years ###
timepoints(fit3,times=c(0,250,500,750,1000,1250,1500))

### plotting the CIF curves using the plot.cuminc function ###
plot.cuminc(fit3,ylab='CUMULATIVE INCIDENCE FUNCTION',curvelab=c('PVR','Reop'),
xlab='Time to first event (days)')
title(main='Aphakic/pseudophakic subtrial')

### performing the Gray's test for both event of interest and competing risk event ###
fit4=cuminc(aphak$firsteventtime,aphak$evtNoReamo,aphak$OP,cencode=0)
fit4
timepoints(fit4,times=c(0,250,500,750,1000,1250,1500))

### plotting the CIF curve for event 1 by treatment group from the Gray's test ###
forplev4=list(list(fit4$'Primary vitrectomy 1'$time,fit4$'Primary vitrectomy 1'$est),
list(fit4$'Scleral buckling 1'$time,fit4$'Scleral buckling 1'$est))
forplev4

plot.cuminc(forplev4,curvlab=c('Primary vitrectomy','Scleral buckling'),lty=c(1,2),
 xlab='TIME TO PVR_BorC (days)', ylab='PROBABILITY FOR FAILURE (from PVR_BorC)')
 title(main='APHAKIC SUBTRIAL:CIFs for failure from PVR STAGE B or C')

### Writing the P-values on the graphs ###
```

```
text(0,0.75,adj=0,paste("Log-rank test:p-value=",round(logRankTestPvalue,3)))
text(0,0.8,adj=0,paste("Gray's test:p-value=",round(fit4$Tests[1,2],3)))

### plotting the CIF curve for event 3,reoperation (the competing event) by treatment group from the
Gray's test ###
forplev3=list(list(fit4$'Primary vitrectomy 3'$time,fit4$'Primary vitrectomy 3'$est),
list(fit4$'Scleral buckling 3'$time,fit4$'Scleral buckling 3'$est))
forplev3

plot.cuminc(forplev3,curvlab=c('Primary vitrectomy','Scleral buckling'),lty=c(1,2),
 xlab='TIME TO 1ST REOPERATION (days)', ylab='PROBABILITY FOR FAILURE (from Reop)')
 title(main='APHAKIC SUBTRIAL:CIFs for failure from Reoperation')

### Writing the P-values on the graphs ###
text(0,0.8,adj=0,paste("Gray's test:p-value=",round(fit4$Tests[2,2],3)))
```

ANALYSIS FOR PVR AS EVENT OF INTEREST AND REOPERATION AS THE ONLY COMPETING EVENT OR AS THE ONLY OTHER EVENT

```
### Reading the dataset phakicFinal.csv into R ###
phak=read.table('D:/Dy/phakicFinal.csv',sep=',',header=T)
phak

### loading the competing risk package ###
library(cmprsk)

### comparing the cause-specific hazard of the marginal distribution of PVR_BorC by the
2 treatment groups ###
fit6=survdiff(Surv(phak$firsteventtime,phak$margPVR)~phak$OP)
fit6
fit1$chisq
logRankTestPvalue2=1-pchisq(fit6$chisq,1)
logRankTestPvalue2

### calculating the CIF estimates for each type of event and the variance ###
fit5=cuminc(phak$firsteventtime,phak$evtNoReamo)
fit5

### obtaining the CIF estimates at any time points say 0,250,500,750,1000,1250,1500 years ###
timepoints(fit5,times=c(0,250,500,750,1000,1250,1500))

### plotting the CIF curves using the plot.cuminc function ###
plot.cuminc(fit5,ylab='CUMULATIVE INCIDENCE FUNCTION',curvelab=c('PVR','Reop'),
xlab='TIME TO FIRST EVENT (days)')
title(main='Phakic subtrial: CIFs for Reoperation(3) and PVR B/C(1)')

### performing the Gray's test for both event of interest and competing risk event ###
fit4=cuminc(phak$firsteventtime,phak$evtNoReamo,phak$OP,cencode=0)
fit4
timepoints(fit4,times=c(0,250,500,750,1000,1250,1500))

### plotting the CIF curve for event 1 by treatment group from the Gray's test ###
forplev4=list(list(fit4$'Primary vitrectomy 1'$time,fit4$'Primary vitrectomy 1'$est),
list(fit4$'Scleral buckling 1'$time,fit4$'Scleral buckling 1'$est))
forplev4

plot.cuminc(forplev4,curvlab=c('Primary vitrectomy','Scleral buckling'),lty=c(1,2),
 xlab='TIME TO PVR_BorC (days)', ylab='PROBABILITY FOR FAILURE (from PVR_BorC)')
 title(main='PHAKIC SUBTRIAL:CIFs for failure from PVR STAGE B or C')
```

```
### Writing the P-values on the graphs ###
text(0,0.75,adj=0,paste("Log-rank test:p-value=",round(logRankTestPvalue2,3)))
text(0,0.8,adj=0,paste("Gray's test:p-value=",round(fit4$Tests[1,2],3)))

### plotting the CIF curve for event 3,reoperation (the competing event) by treatment group from the
Gray's test ###
forplev5=list(list(fit4$'Primary vitrectomy 3'$time,fit4$'Primary vitrectomy 3'$est),
list(fit4$'Scleral buckling 3'$time,fit4$'Scleral buckling 3'$est))
forplev5

plot.cuminc(forplev5,curvlab=c('Primary vitrectomy','Scleral buckling'),lty=c(1,2),
 xlab='TIME TO 1ST REOPERATION (days)', ylab='PROBABILITY FOR FAILURE (from Reop)')
 title(main='PHAKIC SUBTRIAL:CIFs for failure from Reoperation')

### Writing the P-values on the graphs ###
text(0,0.8,adj=0,paste("Gray's test:p-value=",round(fit4$Tests[2,2],3)))
```

ANALYSIS FOR REAMOTIO AS EVENT OF INTEREST AND REOPERATION AS THE ONLY COMPETING EVENT OR AS THE ONLY OTHER EVENT

```
### Reading the dataset aphakicFinal.csv into R ###
aphak2=read.table('D:/Dy/aphakicFinal.csv',sep=',',header=T)
aphak2

### loading the competing risk package ###
library(cmprsk)
### comparing the cause-specific hazard of the marginal distribution of
Reamotio by the 2 treatment groups ###
fit1=survdiff(Surv(aphak2$firsteventtime,aphak2$margReamo)~aphak2$OP)
fit1
fit1$chisq
logRankTestPvalue=1-pchisq(fit1$chisq,1)
logRankTestPvalue

### calculating the CIF estimates for each type of event and the variance ###
fit3=cuminc(aphak2$firsteventtime,aphak2$evtNoPVR)
fit3

### obtaining the CIF estimates at any time points say 0,250,500,750,1000,1250,1500 years ###
timepoints(fit3,times=c(0,250,500,750,1000,1250,1500))

### plotting the CIF curves using the plot.cuminc function ###
plot.cuminc(fit3,ylab='CUMULATIVE INCIDENCE FUNCTION',curvelab=c('Reamo','Reop'),
xlab='TIME TO FIRST EVENT (days)')
title(main='Aphakic/pseudophakic subtrial')

### performing the Gray's test for both event of interest and competing risk event ###
fit4=cuminc(aphak2$firsteventtime,aphak2$evtNoPVR,aphak2$OP,cencode=0)
fit4
timepoints(fit4,times=c(0,250,500,750,1000,1250,1500))

### plotting the CIF curve for event 1 by treatment group from the Gray's test ###
forplev4=list(list(fit4$'Primary vitrectomy 2'$time,fit4$'Primary vitrectomy 2'$est),
list(fit4$'Scleral buckling 2'$time,fit4$'Scleral buckling 2'$est))
forplev4

plot.cuminc(forplev4,curvlab=c('Primary vitrectomy','Scleral buckling'),lty=c(1,2),
 xlab='TIME TO REAMOTIO (days)', ylab='PROBABILITY FOR FAILURE (from Reamotio)')
 title(main='APHAKIC SUBTRIAL:CIFs for failure from retinal detachment')
```

```
### Writing the P-values on the graphs ###
text(0,0.75,adj=0,paste("Log-rank test:p-value=",round(logRankTestPvalue,4)))
text(0,0.8,adj=0,paste("Gray's test:p-value=",round(fit4$Tests[1,2],4)))

### plotting the CIF curve for event 3,reoperation (the competing event) by treatment group from the
Gray's test ###
forplev5=list(list(fit4$'Primary vitrectomy 3'$time,fit4$'Primary vitrectomy 3'$est),
list(fit4$'Scleral buckling 3'$time,fit4$'Scleral buckling 3'$est))
forplev5

plot.cuminc(forplev5,curvlab=c('Primary vitrectomy','Scleral buckling'),lty=c(1,2),
 xlab='TIME TO 1ST REOPERATION (days)', ylab='PROBABILITY FOR FAILURE (from Reop)')
 title(main='APHAKIC SUBTRIAL:CIFs for failure from Reoperation')

### Writing the P-values on the graphs ###
text(0,0.8,adj=0,paste("Gray's test:p-value=",round(fit4$Tests[2,2],3)))
```

ANALYSIS FOR REAMOTIO AS EVENT OF INTEREST AND REOPERATION AS THE ONLY COMPETING EVENT OR AS THE ONLY OTHER EVENT

```
### Reading the dataset phakicFinal.csv into R ###
phak2=read.table('D:/Dy/phakicFinal.csv',sep=',',header=T)
phak2

### loading the competing risk package ###
library(cmprsk)

### comparing the cause-specific hazard of the marginal distribution of REAMOTIO by the
2 treatment groups ###
fit6=survdiff(Surv(phak2$firsteventtime,phak2$margReamo)~phak2$OP)
fit6
fit6$chisq
logRankTestPvalue2=1-pchisq(fit6$chisq,1)
logRankTestPvalue2

### calculating the CIF estimates for each type of event and the variance ###
fit5=cuminc(phak2$firsteventtime,phak2$evtNoPVR)
fit5

### obtaining the CIF estimates at any time points say 0,250,500,750,1000,1250,1500 years ###
timepoints(fit5,times=c(0,250,500,750,1000,1250,1500))

### plotting the CIF curves using the plot.cuminc function ###
plot.cuminc(fit5,ylab='CUMULATIVE INCIDENCE FUNCTION',curvelab=c('Reamo','Reop'),
xlab='TIME TO FIRST EVENT (days)')
title(main='Phakic subtrial: CIFs for Reoperation(3) and Reamotioness(2)')

### performing the Gray's test for both event of interest and competing risk event ###
fit7=cuminc(phak2$firsteventtime,phak2$evtNoPVR,phak2$OP,cencode=0)
fit7
timepoints(fit7,times=c(0,250,500,750,1000,1250,1500))

### plotting the CIF curve for event 1 by treatment group from the Gray's test ###
forplev5=list(list(fit7$'Primary vitrectomy 2'$time,fit7$'Primary vitrectomy 2'$est),
list(fit7$'Scleral buckling 2'$time,fit7$'Scleral buckling 2'$est))
forplev5

plot.cuminc(forplev5,curvlab=c('Primary vitrectomy','Scleral buckling'),lty=c(1,2),
 xlab='TIME TO REAMOTIO (days)', ylab='PROBABILITY FOR FAILURE (from reamotio)')
 title(main='PHAKIC SUBTRIAL:CIFs for failure from Retinal detachment')
```

```
### Writing the P-values on the graphs ###
text(0,0.75,adj=0,paste("Log-rank test:p-value=",round(logRankTestPvalue2,3)))
text(0,0.8,adj=0,paste("Gray's test:p-value=",round(fit7$Tests[1,2],3)))

### plotting the CIF curve for event 3,reoperation (the competing event) by treatment group from the
Gray's test ###
forplev6=list(list(fit7$'Primary vitrectomy 3'$time,fit7$'Primary vitrectomy 3'$est),
list(fit7$'Scleral buckling 3'$time,fit7$'Scleral buckling 3'$est))
forplev6

plot.cuminc(forplev6,curvlab=c('Primary vitrectomy','Scleral buckling'),lty=c(1,2),
 xlab='TIME TO 1ST REOPERATION (days)', ylab='PROBABILITY FOR FAILURE (from Reop)')
 title(main='PHAKIC SUBTRIAL:CIFs for failure from Reoperation')

### Writing the P-values on the graphs ###
text(0,0.8,adj=0,paste("Gray's test:p-value=",round(fit7$Tests[2,2],3)))
```

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Adedoyin Adedipe

Datum: **30.08.2007**