Meta-analysis of Time to Seizure Relapse After a Post-operative Epilepsy Surgery

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Meta-analysis of Time to Seizure Relapse After a Post-operative Epilepsy Surgery

by

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19 March 2020

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Abstract

Epilepsy is a common disease world-wide whose suggested treatment vary from surgical to non-surgical. Although surgical treatments may be commonly recommended and successful in pharmacoresistant epilepsy for patients with refractory epilepsy, there are some patients who experience a seizure relapse. It is of interest to medical practitioners to determine how long patients survive epilepsy after a successful surgery. Survival analysis methods have been used to model time-to-event data. Hence we attempt to determine the time to a seizure relapse in epilepsy patients after a surgery. However, single study have some limitations, such as lack of accommodation of spatial factors, different research approaches to mention a few. Most of the time, single studies are under-powered to detect the factors of covariates. Meta-analysis methods have been developed to overcome this problem, where a number of studies are amalgamated and a common conclusion is drawn. This thesis aims is to determine the long-term seizure outcome after an epilepsy surgery of refractory epilepsy without focusing on the types of refractory but rather in resective surgery. In the current study a systematic review was done using Google Scholar, **Medline**, and **PubMed**. The event of interest is seizure relapse and our interest is to pool the time to first seizure relapse after surgical treatment. To measure the seizure freedom the clinical method call Engel class I was used. The univariate and meta-survival of fixed and random effect model were used to measure the proportion of seizure freedom. Our focus was only in single arm treatment (surgical treatment) . There were a total of 18 studies that satisfy the inclusion criteria with observations at 6 time points measured in months after post-operative (6, 12, 24, 36, 60 and 120 months). In the univariate analysis, the probabilities of seizure freedom of the fixed effects models were systematically larger than the random effect results. There was evidence of significance of heterogeneity between studies, and the true variation between studies test was large. The result that we got in univariate random effect model were for time-points 6, 12, 24, 36, 60 and 120 months were 0.74 95% confidence interval (CI)(0.66- 0.82), 0.69 95% CI (0.61- 0.77), 0.64 95% CI (0.56- 0.71), 0.60 95% CI (0.52- 0.68), 0.56 95% CI (0.48- 0.63) and 0.47 95% CI (0.38- 0.56) respectively. The meta-survival analysis also systematically showed that, the seizure free probability

were larger in a fixed effects model than in a random effects model. The summary survival estimates of the random effect model that were pooled in the following time points 6, 12, 24, 36, 60 and 120 were 0.7655 95% CI (0.6808- 0.8613), 0.7140 95% CI (0.6246- 0.8163), 0.6462 95% (0.5614, 0.7438), 0.6105 95% (0.5225, 0.7133), 0.5700 95% (0.4892, 0.6641) and 0.4755 (0.4078, 0.5545) respectively. The median time to relapse was found using the meta-survival analysis in random effects model to be 104.46 months (8.87 years). We can conclude that the meta-survival analysis may be the method to pool the time-to-event data in one-arm treatment..

Keywords: Refractory epilepsy, long-term seizure, meta-analysis, univariate, meta-survival analysis

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Introduction

1.1 Chapter overview

This chapter overviews and presents literature on epilepsy and how it threatens the quality of life in individuals and in the world at large, especially in developing countries. It also reviews drug resistant epilepsy (DRE) as well as the treatments that are available. Furthermore, it outlines the motivation of the thesis; research question; justification of the study; and the aims and objectives of the study.

1.2 Background information of epilepsy

1.2.1 Introduction to epilepsy

Epilepsy is the most common and dilapidating neurological disorder (Hirtz et al., 2007) that affected approximately 22 million people by 2013 world-wide (Vos et al., 2016). It affects 1% of people in their 20s and 3% of those in their 75s (Browne & Holmes, 2008). It is more common in males than in females, although there are few data from developing countries (Newton & Garcia, 2012; Neligan et al., 2012). Epilepsy patients are at an increasing death risk-between 1.6 and 4.1 (which is expressed as a standardized mortality ratio) which is larger than the general population (Hitiris et al., 2007; Shorvon et al., 2015a). Those cases of death can be caused by the underlying causes of seizure, status epilepticus, suicide, trauma or sudden unexpected death (Hitiris et al., 2007). The risk of suicide is also reported as being much higher for those with epilepsy (Bagary, 2011; Mula & Sander, 2013)) compared to non-epilepsy individuals.

A seizure may be a transient incidence of signs and/or symptoms because of abnormal excessive or synchronous neuronic activity within the brain (Fisher et al.,

2014). The term transient is used as demarcated in time, with a clear beginning and completion (Trinka et al., 2015). Epilepsy is, therefore, a group of neurological diseases characterized by epileptic seizures (Fisher et al., 2014; Chang & Lowenstein, 2003; WHO, 2016) that may vary briefly, and nearly undetectable, to prolonged periods of vigorous shaking (WHO, 2016). In several cases, the explanation for brain disease is unknown however are often genetically or acquired, with the interaction of things like traumatic brain injury, stroke, head tumors, single genetic disease (1-2%) or brain disorders (Berkovic et al., 2006; Pandolfo, 2011; Aminoff et al., 2012).

Fisher et al. (2014) as a neurological disorder which will be attributed a minimum of one in every of these conditions: a minimum of 2 unwanted seizures occur within the course of a day; one unprovoked sseizure and a likelihood of any seizures just like general repeat risk a minimum of 60% after two unprovoked seizures, occurring over the next ten years. This can be used for the diagnosis of epilepsy.

Epilepsy is not preventable (Zaidi et al., 2000) but to know the definition, classification, syndrome, and test, can be helpful with the diagnosing (managing) epilepsy (Zaidi et al., 2000; Akhtar, 2002; Engel et al., 2013; Wilden & Cohen-Gadol, 2012; WHO, 2016). In many cases, the treatment to be given to the patient is determined based on these characteristics. Although medication can control the successful management of 70% cases (Eadie, 2012), treatment in the developing world is still low. Approximately 75% of epilepsy patients are either untreated or not appropriately treated (WHO, 2016). Approximately 90% of epilepsy patients do not receive medication either due to unavailability of treatments or it is too expensive for the government to make it available for free to the public (WHO, 2016). There are also epilepsies that are not easy to diagnose.

1.2.2 Epilepsy in the developing world

In a study done by Seneneyake & Román (1993) for developing countries, it had been found that epilepsy was high in Latin America, Liberia, Nigeria and the United Republic of Tanzania. Most significantly, the etiology issue was parasitic infection common in tropical countries and a few elements of Africa; and infection of bacteria, viral origin, perinatal brain damage, head injury, toxic agent and heredity factors were important in explaining the high prevalence of epilepsy.

Newton & Garcia (2012) and Birbeck et al. (2002) noted that there's a treatment gap within the health care of every and each country within the developing world, principally for those between urban dwellings and rural areas. This could be as a

result of, in urban areas, there's easier access to health facilities than outside urban areas. The shortage of brain disease medical specialty facilities in several developing countries and few neurologists to assess those with brain disease and restricted electroencephalography (EEG) testing, X-ray X-raying (CT) scans, and Magnetic resonance imaging (MRI) to verify diagnoses of brain disease(Birbeck et al., 2002) also contribute to the poor diagnosis of epilepsy.

1.2.3 Impact of epilepsy in quality of life

The quality of life (QOL) is largely the health of people and communities (Barcaccia, 2013). This may be outlined by characteristics that ar noticeable in fulfillment of life (where these options ar taken as important) for instance, physical health, family, education, employment, wealth, spiritual beliefs and therefore the atmosphere (Barcaccia, 2013).

Epilepsy is attended with profound physical, psychological and social consequences and also the impact of uncontrolled brain disorder on a personality's quality of life is bigger than that of another chronic conditions, like diabetes, cancer or cardiovascular disease to mention the few (Reynolds, 2001). Many studies have found that the upper the seizure severity the lower the standard of life, particularly in social living (Harden et al., 2007; Téllez-Zenteno et al., 2005; Wieser & Hane, 2003; Gholami et al., 2016; Seneneyake & Román, 1993).

Gholami et al. (2016) argue that with correct epilepsy management, more than three-quarters of individual with epilepsy can get regular health and even get seizure freedom. Features that are essential when explaining the impact of epilepsy on quality of life are: education (especially for individuals who previously received inadequate schooling); employment (unemployment in people living with epilepsy is 2 to 3 times higher than people living with other disabilities) and independence (people with epilepsy may have experienced some physical disability which may limit their independence) (Gholami et al., 2016).

1.2.4 Drug resistant epilepsy

Although epilepsy can be treated using drugs, such as anti-epileptic drug (AED), this is also a fact that there are other drug resistant epilepsy (DRE). This is also known as refractory epilepsy or pharmacoresistant epilepsy, which is defined as the failure of adequate trials of two dosages controlled and appropriately chosen anti-epileptic drug (AED) to support seizure freedom (Kwan et al., 2010). The important reason for using treatment to control seizure is to achieve seizure freedom which is better

for maintaining the quality of life and cognitive function (Elger & Schmidt, 2008). It can be estimated that one third of patients with epilepsy are drug-resistant (Brodie, 2013). To maintain the quality of life in the patient with epilepsy it is recommended that any treatment to control seizures or achieve seizure freedom should be used.

The most suggested treatment to treat drug resistant epilepsy is epilepsy surgery which can be either a resective or disconnective procedure (Clinic, 2018). According to (Bromfield et al., 2006; Clinic, 2018; Engel et al., 2013) the resective procedure, is the removal of the part of the brain that causes the seizure is performed, while in the disconnective procedure, the neural connections in the brain that allows the seizure to spread are disconnected. Any patients can be referred by their physician to any epilepsy center for pre-surgery evaluation. The magnetic resonance tomography is used as the imaging technique, and to pinpoint the focus of epileptic seizure the electrocorticography is used.

Even though the surgical treatment seems successful in refractory epilepsy patients, it is not 100 % effective in achieving seizure freedom (Engel, 2013, 1993). In recent studies, it was found that seizure freedom varies with types of surgery. Sirven (2013) mentioned that 30 - 50 % of patients achieved seizure freedom while in 20 - 40 % who had epilepsy recurrence post-operative patients, the seizure is reduced at least by 90 % and at least 70 % of patients achieved seizure diagnosed with AED. In temporal lobectomy about 60 - 70 % achieved seizure freedom, and in 20 - 25% of those with epilepsy recurrence, the seizure will be reduced by 85 % (Téllez-Zenteno et al., 2005). As such, this study is more focused on investigating the seizure freedom over time after surgery where the event of interest is the first recurrence of seizure post-operative.

Tetto et al. (2002) mention that in Italy they found that the annual cost for seizure treatment is 412 Euros, 2198 Euros for drug resistant patients and 945 euros for surgical candidates. It is clear that surgical treatment more expensive than that of non-drug resistant epilepsy, but drug resistant candidate epilepsy costs triple the price of surgical treated epilepsy (Begley & Beghi, 2002; Tetto et al., 2002). This puts a strain on the economy, especially on those countries where treatment is provided by the government.

1.3 Research motivation

Although surgery might be the most recommended treatment, it may have some unforeseen drawbacks. Relapse is one of the undesired outcomes of a seizure opera-

tion. Sometimes it is a result of an unsuccessful surgery. Unsuccessful surgery might be caused by surgery heterogeneity , incorrect localizing or incomplete resection of the seizure focus or progression of underlying disease.

This study is focused on determining time until relapse of seizure post-operative. The statistical method that is mostly used to determine time-to- event is survival analysis. It has an advantage of the ability to handle the censored events. However, single studies have been proved to have their own disadvantage (Ishak et al., 2007; Borenstein et al., 2009; Taghavi, 2014; Arends et al., 2008; Rosenthal, 1991). The introduction of meta-analysis methods addresses this problem as such Glass (1976); Glass et al. (2009); Simpson & Pearson (1904) proposed to integrate studies to investigate how to increase the chance of controlling epilepsy and educate those affected and/ or infected by epilepsy to be aware of other treatments of epilepsy. This will help to inform policy makers in their decision making regarding epilepsy; hence contribution to the body of knowledge regarding the factors associated with death by epilepsy and the other available treatment for refractory epilepsy .

1.4 Research questions

Since the surgical treatments are much more costly compared to the non-drug resistant epilepsy we would expect them to be more difficult to access even if possibly more effective. It is important to find out how effective they are. The following questions might arise: can government invest in this kind of treatment to achieve a better quality of life in individuals? Specifically, is there a chance that after a surgical treatment, the patient may relapse? If so, what is the median (survival) time to relapse? What factors are associated with relapse?

1.5 Study justification

The focus of the study in determining if surgical treatment has a long-term or lifelong effect by combining the studies that investigate the same matter. Meta-analysis is the statistical method that is introduced to combine different studies to determine the consistency of these studies (Ishak et al., 2007; Borenstein et al., 2009; Arends, 2006). If there is consistency, the efficiency of surgical epilepsy treatment can be concluded.

1.6 Aims and objectives

The main objectives of the study are to:

1) Combine studies that focus on the long-term outcomes that are important after brain epilepsy surgery.

2) Consider studies that meet the inclusion criteria. That can be analysed using a meta-analysis approach.

3) Overview of the survival analysis when following up epilepsy patients after surgery in each of the studies, that is, those studies that use seizure freedom on patients and determine which statistical effect sizes (like odds ratio, hazard ratio, and so on) were used to analyse the results.

4) Meta-analysis will be used to determine the pool proportion of survival (seizure freedom) post-surgery, using the inverse variance weight as well as determinants of seizure relapse.

5) Test for inter-variation in those included studies.

6) Determine the long-term success of epilepsy surgery.

7) Determine the median time to relapse from epilepsy surgery

1.7 Structure of the study

Chapter one we were reviewing the background of epilepsy, research questions, resarch motivation, research justification and the aims and objectives of the research. In chapter two reviews the survival analysis for both the classic and its current modifications. In chapter three the study reviews the meta-analysis statistical method which is the standard method (fixed and random effects model) that will play a key role in achieving research goals. Chapter four discusses how a systematic review was carried out as well as descriptive statistics. Statistical software that will be used to analyse the data is stated. Chapter five and six gives the result from the analysed data. Chapter seven gives the conclusion of the study and possible future work.

1.8 Summary

In this chapter, we were reviewing the background of epilepsy (especially, the definition of epilepsy, epilepsy in the developing world, refractory epilepsy and cost of epilepsy). We also discussed the research question, motivation of research, research justification and the aims and objectives of this thesis. At the end of this chapter, the structure of this thesis was discussed. Most of this background will play an important role when we analyzed and draw the conclusion of this research.

Chapter 2

Survival analysis in epilepsy

In this chapter, an overview of survival analysis and its importance in epilepsy studies will be done. Survival analysis can be used to determine how long it takes patients to have the first seizure after surgery in the context of time-to-event analysis.

2.1 Overview of survival analysis

Survival analysis is a statistical tool that can be used when time-to-event needs to be modeled with longitudinal data (Collett, 2015; Allison, 2010). It is preferred due to its ability to handle censored data, time-dependent variables and is suitable for longitudinal data. Most importantly rather treating the event of interest as a binary outcome the analysis also takes the time-to-event into account. In the case of censoring, a technique is devised that associates the information in the censored and non-censored cases in a way that produces a consistent estimates.

Survival analysis uses data in the form of times from a well-distinct time origin until the occurrence of an event of interest (Clayton, 1978). Such events are generally referred to as failure or end-point where the time can be measured in days, weeks, years and so on (Collett, 2015). The Time origin is usually the beginning of the study before the event of interest occurs. A subject is followed over a specific period of time until the event of interest occurs, or until the subject is censored, or until the end of the study. Allison (2010) explains it as a qualitative change that can be positioned in time where the qualitative change is a transition from one discrete state to another. In the application of survival analysis, the time of change occurrence (event) must be known. A transition occurs instantaneously that will make the actual time of onset unknown. The best observation plan is prospective for survival analysis, where you begin observing a set of individuals at some well-defined point of time and you follow them for some substantial period of time, taking the time at which the

event occurs into consideration (Allison, 2010). In this study we are interested in time to seizure relapse after an epilepsy surgery. The time to event of interest will start ticking at day of surgery, and subjects who do not experience a relapse are considered to be censored.

2.2 Features of survival data

The survival data can be collected over a long period of time (longitudinal data) and it can be about timing of an event or time to event data (Allison, 2010; Kaplan & Meier, 1958; Kleinbaum & Klein, 2010). Mostly in biostatistics, the data arises from cohort studies, clinical trials or intervention studies. The most important elements in survival analysis are: time of origin, the event of interest and the time between them (these terms may vary depending on the author but their meaning is the same) (Clayton et al., 1993; Collett, 2015)). Survival data is non-normal data, which contains time dependent variables, and since it is from the follow-up studies in most cases it contains censored events.

2.2.1 Non-Normal data

Most cases of survival data arise from observation of individuals from the onset of risk until the event occurs (Vaupel et al., 1979). The event may occur between the time of origin and the end of follow-up. At the beginning of the study, the survival probability is 100% but as some individual experience the event, the probability of survival continues reducing. This results in positively skewed data, thus violating the assumption of normality which is required by most standard statistical methods (Allison, 2010). It is also seems impossible to model survival data using the dichotomous method, since its interest is to model the occurrence of an event only. The best technique that has been designed to model this kind of data is survival analysis, which also has the ability to handle time-dependent variables (Kleinbaum & Klein, 2010).

2.2.2 Censoring

The second distinct feature of survival data is censoring. For uncensored outcome it means the event of interest has occurred for such individuals and their waiting time for the event of interest is known, while if an individual is censored for the event all we know is that waiting time exceeds the observed time (Allison, 2010; Vaupel et al., 1979). Since this is always the case in longitudinal data (because of drop out, or the study end before some individuals experience the event), there must be a better

method of handling censored events. Allison (2010) stated that it is important to handle censoring events in the analysis, to avoid biased parameter estimates.

There are three types of censoring (Kleinbaum & Klein, 2010) namely:

i) Right censoring is when the event occurs after the observed time. In this case, the censoring time is less than the actual survival time. It is usually a result of dropout or study ending before observing the event.

ii) Left censoring is when the event happened before the beginning of the study; here the actual survival time is less than the observed censoring time.

iii) Interval censoring occurs when the event is known to have happened in an interval of time but the actual survival time is not known.

2.3 Survival analysis common terminology

The two most important terms that are used to explain the time of occurrence of an event, are survival function and hazard function.

2.3.1 Survival function

The survival time can be defined as the measured length of time from a specific time origin until the event of interest occurred (Kleinbaum, 1998) (time of epilepsy surgery can be regarded as time origin). The main concept in survival analysis is to model the time to event, which we can call survival time (Wienke, 2010). Therefore the survival function gives the probability that an individuals survives longer than some specified time (Allison, 2010; Kleinbaum, 1998; Wienke, 2010). For example the probability of a patients having seizure relapse after a brain surgery being longer than time t. It is important, before analysing the survival data to know time origin, time interval of observation and the definition of an event must be clear.
For a group of individuals $i = 1, 2, ..., n$ with actual survival times $t_1, t_2, ..., t_j, ..., t_n$, these can be regarded as the observed values of a random variable T, which takes non-negative values. The survival function, $S(t)$ gives the probability that the random variable T exceeds the specified time t (Kleinbaum & Klein, 2010; Cox, 1972). This is given by:

$$S(t) = P(T > t) = 1 - F(t) \tag{2.1}$$

where $F(t)$ is the cumulative density function. Since $S(t)$ is the probability of surviving beyond time t, it should be noted that survival when $t = 0$, is 1 (that is $S(0) = 1$)

and as $t \to \infty$, $S(t) \to 0$. It is a positively skewed function that can be estimated using the Kaplan-Meier estimation (Wienke, 2010; Kaplan & Meier, 1958).

2.3.2 Hazard function

The hazard function gives the instantaneous failure rate at time t given that the individual has survived up to time t. It is given by:

$$\lambda(t) = \lim_{\Delta t \to 0} \frac{1}{\Delta t} P(t \leq T \leq t + \Delta t | T \geq t) \tag{2.2}$$

The cumulative hazard function can then be given as:

$$\Lambda(t) = \int_0^t \lambda(u) du \tag{2.3}$$

2.3.3 Relationship of Survival and Hazard Function

The hazard and survival functions can be estimated from the observed data (Clayton et al., 1993; Collett, 2015). The relationship that we are going to discuss is between $S(t)$, $f(t)$ and $\lambda(t)$ showing that if one of these functions is given you can be able to obtain the other functions. When dealing with continuous variables the probability density function is given by

$$f(t) = \lim_{\Delta t \to 0} \frac{1}{\Delta t} P(t \leq T \leq t + \Delta t) = F^{'}(t) = -S^{'}(t) \tag{2.4}$$

hence from equation 2.4 it can be shown that hazard rate at time t is given by

$$\frac{-d}{dt}[\log(S(t))] = -\left[\frac{1}{S(t)}\right] S^{'}(t) = \frac{f(t)}{S(t)} = \lambda(t) \tag{2.5}$$

since we know that:

$$\Lambda(t) = \int_0^t \lambda(u) du = \int_0^t \frac{f(u)}{S(u)} du = \int_0^t \frac{-d}{du}[\log(S(u))] = -\log(S(t))$$

hence

$$S(t) = e^{-\Lambda(t)}$$

2.4 Estimation methods

The survival and hazard function discussed in section 2.3 above can be estimated in three ways, namely: non-parametric, semi-parametric and parametric methods.

2.4.1 Non-parametric estimation

The non-parametric estimation can be used to explore and describe the time to event data, without putting any constraints on the data with no assumption about any specific parametric distribution (Allison, 2010; Kleinbaum, 1998).

Kaplan-Meier estimation

In a single sample of survival times, where none of the observation is censored, survival function can be estimated by the empirical survival function which is defined as:

$$\hat{S}(t) = \frac{\text{number of individual with}(T \geqslant t)}{\text{total sample size}}.$$

It is assumed to be constant between two adjacent event times and the plot of estimated survival function against t is a step function and the function decreases after each observed survival time. However, when there are censored observations, we introduce the method that can handle the censoring correctly; which is a non-parametric method for estimating survival function, proposed by Kaplan & Meier (1958) also called product limit or Kaplan Meier estimate. This, in fact, is the non-parametric maximum likelihood that gives rigid a theoretical justification. The Kaplan-Meier method estimates the survival function when an event occurs but also fakes account of censoring by adjusting the risk set appropriately (Wienke, 2010). Suppose we have $A_1, A_2, ...A_k$ different events, the probability of all k events occurring together, can be written as the product of conditional probabilities.

$$P(A_1 \cap A_2 \cap ... \cap A_k) = P(A_k|A_{k-1} \cap A_{k-2} \cap ... \cap A_1)(A_{k-1}|A_{k-2} \cap A_{k-3} \cap ... \cap A_1) \times .....(A_2|A_1)P(A_1)$$

In the estimate $S(t)$ let us suppose that $a_k < t \leq a_{k+1)}$ then:

$$\begin{aligned}
S(t) &= P(T \geq a_{k+1}) \\
&= P(T \geq a_1, T \geq a_2, ..., T \geq a_{k+1}) \\
&= P(T \geq a_1) \prod_{j=1}^{k} P(T \geq a_{j+1}|T \geq a_j) \\
&= \prod_{j=1}^{k} [1 - P(T = a_j|T \geq a_j)] \\
&= \prod_{j=1}^{k} [1 - \lambda_j]
\end{aligned}$$

let d_j denote the number of events at time a_j, and r_j is the number at risk at time a_j,

then the product limits formula can be given by:

$$\hat{S}(t) \cong \prod_{j=1}^{k} \left[1 - \frac{d_j}{r_j}\right] = \prod_{j:a_j<t}^{k} \left[1 - \frac{d_j}{r_j}\right] \tag{2.6}$$

Even though it is a non-parametric estimate like all likelihood estimates, the variance must also be estimated. Collett (2015) shows that variance is derived using the delta method leading to what is known as the Greenwoods formula and is given as:

$$\hat{V}ar\hat{S}(t) = [\hat{S}(t)]^2 \sum_{j:\tau_j<t} \frac{d_j}{(r_j - d_j)r_j} \tag{2.7}$$

Once the survivor function is estimated one can determine the median survival time as maximum t_m such that $\hat{S}(t_m) \leq 0.5$.

Life tables

The life table estimator of the survival function is used when one is faced with aggregated data instead of individual survival times as for the Kaplan-Meier estimator(Collett, 2015). The product limit formula can be used as we did with the K-M equation 2.6, but there is a need to specify the number of individuals at risk, (r_j, in the time interval $(t_{j-1}, t_j,)$). Denote censoring events at this $(t_{j-1}, t_j,)$ interval as c_j, then we can assume that half of the individuals were censored at the start of the year and half at the end. Then number at risk can be modified as:

$$r'_j = r_j - \frac{c_j}{2} \tag{2.8}$$

and the probability of failure in an interval $(t_{j-1}, t_j,)$ is estimated by :

$$p_j = \frac{d_j}{r'_j} \tag{2.9}$$

The probability of surviving the interval $(t_{j-1}, t_j,)$ is $(1 - p_j)$, so the probability of surviving up to the end of interval $(t_{j-1}, t_j,)$ is:

$$\hat{S}(t) = \prod_{j:a_j<t}^{k} \left[1 - \frac{d_j}{r'_j}\right] \tag{2.10}$$

Nelson-Aalen estimation of cumulative hazard

The Nelson-Aalen estimator of the cumulative hazard function is given by

$$\hat{\Lambda}(t_j) = \sum_{j=1} \lambda_j \delta \tag{2.11}$$

which is the summation of product of the value of hazard in j^{th} interval and δ is the width of each intervals. Since the $\lambda_j \delta$ can be taken as the probability of the event occurring in the interval, we can further say

$$\hat{\Lambda}(t_j) = \sum_{j=1} \frac{d_j}{r_j} \tag{2.12}$$

$$\hat{\Lambda}_{\mathbf{NA}}(t) = \sum_{j:r_j<t} \frac{d_j}{r_j} \tag{2.13}$$

.

2.4.2 Semi-parametric estimation

The semi-parametric model has non-parametric and parametric model components. An example of the semi-parametric method that is popular is the Proportional Hazard Model (PHM) which was first developed by Cox (1972). It is a multivariate technique for analyzing the effect of two or more variables on survival. It has commonly been used in most analyses to build the determinants of risk of occurrence of an event. The assumption underlying this model is that there is a hazard at the duration of the occurrence of an event (Trussell & Bloom, 1983).

The hazard function for individual i is written as :

$$h_i(t) = h_0(t) \exp(\boldsymbol{X}_i^T \boldsymbol{\beta}) \tag{2.14}$$

where $h_0(t)$ is the baseline hazard function for an individual whose covariates all have the values of zero. For individual i, $\boldsymbol{X}_i = (x_{i1}, x_{i2}, ..., x_{ip})$ is the vector of p covariates and $\boldsymbol{\beta}$ is the co-efficient associated with each of the p covariates.

Equation 2.14 means that the hazard rate for individual i is the product of two factors:

i) A baseline hazard function $h_0(t)$ that is left unspecified, except that it cannot be negative.

ii) An exponentiated function of a set of vector of covariate.

A measure of the effect of a covariate is determined by the hazard ratio (that is the ratio of two hazard rates). For example, hazard ratio of individuals i and j for a covariate x, like gender, whose regression co-efficient is common β, is given by

$$\frac{h_i(t)}{h_j(t)} = \frac{h_0(t)\exp(x_i^T\beta)}{h_0(t)\exp(x_j^T\beta)} = \exp(\beta(x_i - x_j)) \tag{2.15}$$

which is clearly a function that is free from t (time) only if x is not time-dependent variable. The proportional hazards function has a hazard for any individual which is a fixed proportion of the hazard. Its hazard ratio is not affected by the baseline hazard. So in the equation 2.15 here the $h_0(t)$ cancels out. As a result, the ratio of the hazard is constant over time because the right hand term in equation 2.15 does not vary with time. The graph of the log hazards for individuals i and j, should be strictly parallel. If the hazard ratio is greater than 1 that means the hazard rate of individual i is great than that of j; if the hazard ratio is less than 1 the vice-versa is true; and if the hazard ratio is equal to one that means there is no difference in hazard ratio.

2.4.3 Parametric estimation

As opposed to semi-parametric estimation described in section 2.4.2, where the baseline hazard was left unspecified in parametric estimation, the baseline hazard is assumed to follow some distribution. In parametric estimation of baseline hazard function depends on known statistical distributions that are mainly used in time-to-event data hence maximum likelihood estimation can be used analytically or iteratively. Weibull, Exponential, and Gompertz are some of the well known parametric models that can be used to model the survival time data (Kleinbaum, 1998; Collett, 2015; Allison, 2010). In this subsection there is an overview of those models.

Exponetial Distribution

The hazard function for the exponential distribution is constant, given by

$$h_0(t) = \lambda. \tag{2.16}$$

It is independent over time, which is rarely possible in the real longitudinal data. Since in many known scenarios the event rate increases or decreases over time. In most cases it can be used as the reference distribution to compare it with other distributions in modelling time to event data.

Weibull distribution

The common form of the Weibull distribution is the two parameter Weibull distribution; γ which is known as the parameter that gives shape to the distribution and λ is the scale parameter. The survival distribution can be written as.

$$S(t) = e^{-\lambda t^{\gamma}} \tag{2.17}$$

and hence

$$h_0(t) = \gamma \lambda t^{\gamma - 1} \tag{2.18}$$

As explained in Table 2.1 $\gamma = 1$ the distribution will reduced to exponential distribution with only scale parameter λ.

Table 2.1: Different shape of hazard rate

Values of γ	Shape of $h(t)$
$0 < \gamma < 1$	exponential decay
$\gamma = 1$	constant hazard rate
$\gamma > 2$	exponential growth
$\gamma = 2$	straight line

Gompertz distribution

The Gompertz hazard function can also be used when the interest of the study is to model the failure time: the survival function of the Gompertz can be written as:

$$S(t) = exp\left(\frac{\lambda_0}{\theta}(1 - e^{\theta t})\right) \tag{2.19}$$

thus the hazard function can be written as:

$$h(t) = \lambda_0 e^{\theta t} \tag{2.20}$$

where the domain of t is $(0, \infty)$ and the $\lambda_0 > 0$, denotes the hazard rate that is constant over time. The θ denotes the shape of hazard function, and if $\theta = 0$ the hazard function is reduce to that of exponential distribution, that makes the exponential hazard function a special case of Gompertz Distribution; when $\theta < 0$ as in Weibull hazard function, it decrease monotonically; and when $\theta > 0$ the hazard rate increases. It can be noted that $log(h(t))$ of Gompertz distribution is a linear function

of t.

Regression survival model

Non-parametric methods cannot control covariates. It is essential to have model for covariates since the covariates have some advantages of explaining the condition of survival time. The regression models are interested in modeling the data that includes covariates. These are given:

$$h(t/\boldsymbol{X}) = h_0(t)\eta(\boldsymbol{X}^T\boldsymbol{\beta}) \tag{2.21}$$

where the $\boldsymbol{X}$ is the vector of covariates, $h_0(t)$ is the baseline hazard, $\boldsymbol{\beta}$ is the vector of regression coefficient and $\eta(\boldsymbol{X}^T\boldsymbol{\beta})$ is the link function. In the case where

$$\eta(\boldsymbol{X}^T\boldsymbol{\beta}) = \exp(\boldsymbol{X}^T\boldsymbol{\beta}) > 0, \forall \boldsymbol{X}, \tag{2.22}$$

then equation 2.21 becomes

$$h(t/\boldsymbol{X}) = h_0(t)\exp(\boldsymbol{X}^T\boldsymbol{\beta}) \tag{2.23}$$

Kleinbaum (1998), Allison (2010) and Collett (2015) noted that when the baseline hazard function is being specified, that model will be known as the parametric model and the model takes the name of the assumed distribution. For example, if $h_0(t) = \lambda$ then the regression model will be known as the exponential regression model and it will be given as:

$$h(t/\boldsymbol{X}) = \lambda\exp(\boldsymbol{X}^T\boldsymbol{\beta}) \tag{2.24}$$

if the baseline hazard function is assumed to be $h_0(t) = \gamma\lambda t^{\gamma-1}$ then the regression model is called the Weibull regression model it will be given as :

$$h(t/\boldsymbol{X}) = \gamma\lambda t^{\gamma-1}\exp(\boldsymbol{X}^T\boldsymbol{\beta}) \tag{2.25}$$

, and if the baseline hazard function is assumed to be $h_0(t) = \lambda_0 e^{\theta t}$, then the regression model is called the Gompertz regression model and is given as:

$$h(t/\boldsymbol{X}) = \lambda_0 e^{\theta t}\exp(\boldsymbol{X}^T\boldsymbol{\beta}) \tag{2.26}$$

2.5 Summary

This chapter reviewed some concepts that are crucial in modeling survival time data as it is the classic and the up to date way of modeling time to event data. An individual may be interested in using some of these types of model based on the type

of data and interest of the study. All these models are taken as essential methods on analysing biostatistics problems. These are common methods that most authors use to analyze the time to relapse data in epilepsy that our study is interested in.

Chapter 3

Meta-analysis

Since survival analysis is widely used in analysing the time to a first seizure after an epilepsy surgery. Our interest is in modelling time to relapse after epilespy surgery using meta-analysis methods.

3.1 Introduction to meta-analysis

3.1.1 Limitations of single survival study

In scientific studies, the major aim is always to get better results with less error than previous studies with similar objectives. This is done to ensure that bias and variability in the results is reduced (Cooper et al., 2009; Larry & Ingram, 1985; Cooper, 2015). Single studies are usually under-powered to be able to correctly detect the effect of covariates (Egger et al., 2001). Sometimes if one focuses on just one population, results can be questionable if the methodology was poor. It is natural to want to look at more than one study of similar problem, in order to gain confidence in the result.

3.1.2 Solution of single studies limitation

To increase results with certainty, the method of synthesizing studies with the same problem, with a similar hypothesis, was developed (Cooper et al., 2009). The attempt is to integrate the empirical research for the purpose of creating a generalized result (Cooper et al., 2009). Cooper (2015) defines a combined studies as ”the study that focuses on empirical studies and its goal is to summarize the previous studies and come up with the conclusion from separated studies that address common hypotheses and its interest is to present the state of knowledge with the relation and to highlight any crucial issue that was left unresolved ”. These methods were done from the 17th century (Cooper et al., 2009) but the one that was first published by

Pearson in 1904 was where he used the average to better the typical effect of inoculation of other diseases. He used 5 separate samples for enteric fever and mortality data (Simpson & Pearson, 1904).

3.1.3 Meta-analysis definition

In 1976, Glass (1976) introduced the word meta-analysis, where the term meta is a prefix that means the abstraction from another concept that is used to finish the latter. According to Rothman et al. (2008), we can define meta-analysis as the analysis of analyses that can be illustrated as the statistical analysis that combines the result of multiple scientific studies (Ellis, 2010; Normand, 1999). What we can notice about all those multiple scientific studies, they must have a common purpose of trying to address a similar question (Rothman et al., 2008). Even if they have a common research question but their findings will differ by a certain degree of error (the cause of that might be because of the study methodology, different population, human error, etc) (Ellis, 2010). The aims of the meta-analyst are to try to combine the findings of these studies by using some statistical estimates methods to pool these results. Since there are different degrees of errors, the meta-analyst will yield a weighted average according to the uncertainty in each of the study, this will normally reflect the true population of effect sizes more accurate than any of the individual's estimates on which is used Ellis (2010).

To perform the meta-analysis is very important in a research world to illustrate that, let say the meta-analyst is interested in the clinical hypothesis and want to evaluate it, let say there are base from the published clinical trials articles, meta-analysis can play an important role for summarizing the results of the quantitative literature. Meta-analysis permits the objective assessing of the proof, which can result in resolution of uncertainty and conflict. It will scale back the likelihood of false-negative results and stop undue delays within the introduction of effective treatments into clinical apply Arends (2006). It may also help in prior hypotheses relating to treatment effects in subgroups of patients could also be tested with meta-analysis (Zou et al., 2004).

Some authors have described meta-analyzes as research summaries of research field which describe the general strength of the effect or variety of an item and the statistical significance and the kind of moderator variables that one can predict the strength of the object type (Cooper, 1989; Glass et al., 2009; Larry & Ingram, 1985; Montgomery, 2000; Richard & Pillemer, 1984; Rosenthal, 1991). In additional Rosenthal & DiMatteo (2001) added that meta-analysis is not just a statistical process: be-

cause of the methodology for systematically examining the body of research; the formulation of hypothesis; the way it conducts on searching, establishing exclusion, and inclusion criteria; for recording, and statistical synthesizing, and integrating the effect sizes from these studies; it is a method of searching moderator and mediator variables to explain effect of interest and on reporting the result.

These are some of the reasons why many scientists accepted meta-analysis and used it on a complex studies (Higgins & Green, 2011)

i) Results are often generalized to a larger population..

ii) The precision and accuracy of estimates are often improved as additional information is employed. This, in turn, could increase the statistical power to discover an impact.

iii) Inconsistency of results between studies are often quantified and analyzed. for example, will inconsistency arise from sampling error? Or ar the study results (partially) caused by between-study heterogeneity?

iv) Hypothesis testing are often applied on summary estimates.

v) Moderators are often enclosed to elucidate variation between studies.

vi) The presence of publication bias are often investigated.

These are some of the advantages of meta-analysis (Deeks et al., 2008):

i) It assists people who are not familiar with statistics and also other researchers.

ii) It is accessible to anyone

iii) It provides some knowledge to policymakers

iv) It increases the certainty of the studies, that can increase research funding, and also increases communication among researchers.

Presently meta-analysis is used in epidemiology and in evidence-based medicine (Rothman et al., 2008). However, in medical treatment, it was only published in 1955. The more recent development on the analytical technique is on educational research that was done by (Cooper, 1989; Glass et al., 2009; Larry & Ingram, 1985; Montgomery, 2000; Richard & Pillemer, 1984; Rosenthal, 1991; Rosenthal & DiMatteo, 2001; Taghavi, 2014; Rücker et al., 2009) to mention a few. There are many developments in applications and techniques that make meta-analysis to be taken as an advanced method of researching some interesting matters. That also increased the interest of using meta-analysis in different fields of studies such as psychology, social science, applied statistics, biostatistics, and ecology, to mention a few. It is

because of these reasons that this study focuses on the meta-analysis of studies on survival analysis of time until relapse after epilepsy surgery.

3.2 Effect sizes

The aim of meta-analysis is to search for studies and ask a new question based on the result of those studies (DerSimonian & Laird, 1986; Ishak et al., 2007; Musekiwa et al., 2016). Since meta-analysis is based on analyzing the findings of the different studies it is essential to know the effect sizes. The effect size is the metric used to compare two groups whose magnitude of treatment is required for deliberate intervention (Ishak et al., 2007; Borenstein et al., 2009). The example of effect sizes might be odds ratio or relative risk for binary outcomes, a mean difference for continuous outcomes, or a hazard ratio for survival data. Borenstein et al. (2009) explain the three major steps that must be followed before using effect sizes:

- The effect sizes should be comparable to one another across the study or measure the same effects.
- It should be computable from the source that is reported.
- It should have good technical properties.

The question that is important in presenting the effect sizes is: there is any homogeneity across the studies (Normand, 1999)? If there is, then the fixed effect model is the best model that can be used to analyze the effect sizes; otherwise, the random effect model can be used to analyse the effect sizes. The main assumption of a fixed-effect model is that one true effect sizes across all studies and observed effect sizes will only vary because of the random error in each study (Borenstein et al., 2009; Normand, 1999; DerSimonian & Laird, 1986), that is within-study variation. Since there might be a difference between studies due to sample size and level of sampling error, DerSimonian & Laird (1986) proposed another method of dealing with this issue of variation. The assumption that is made about the variation will allow the variation within a study and variation between studies. This model is called a random effect model (DerSimonian & Laird, 1986).

The goal of synthesizing studies is not only to obtain the summary effect but also to make sense of the effect pattern. This can be achieved by understanding the consistency. If there is any, we consider the right implications for those cases. To understand if there is evidence of variation we need to know the exact value of variance,

the substantive implication of heterogeneity and the proportion of the observed dispersion (Borenstein et al., 2009). This will be done by identifying and quantifying heterogeneity, using the test of significant, Q-test, to test if there is any heterogeneity between the studies; estimating the variance between the studies, and estimating the proportion of variation among the studies using the $I^2 - test$. If it is large, the best option is to use meta-analysis regression to analyze the effects (Normand, 1999).

3.3 Statistical methods of meta-analyisis

Suppose that in all included studies, the survival function is given or observed from the Kaplan-Meier curve with their variance for each and every different time point that each of the studies was analyzed. Using the survival function as the effect sizes, it can be represented in terms of the Table 3.1.

Table 3.1: The survival proportion for each time point per each study

Study	Survival endpoints					
1	$S_1(t_1)$	$S_1(t_2)$	....	$S_1(t_j)$	....	$S_1(t_J)$
2	$S_2(t_1)$	$S_2(t_2)$	....	$S_2(t_j)$	....	$S_2(t_J)$
.						
.						
.						
i	$S_i(t_1)$	$S_i(t_2)$	....	$S_i(t_j)$	....	$S_i(t_J)$
.						
.						
.						
N	$S_N(t_1)$	$S_N(t_2)$	....	$S_N(t_j)$	....	$S_N(t_J)$

Table 3.1 can be interpreted as the proportion of survival of J pre-determined time points for N independent studies. $S_i(t_j)$ indicates the survival proportion for study i at time t_j.

The study pooled the survival proportion for each endpoint separately, and on each of these time points, the classical methods can be applied.This is taken as the easiest way to the survival data.

3.3.1 Estimation of survival proportion variance from confidence interval

In most cases, the studies that may be included may not present the survival proportion variance, but they may present the confidence intervals for each survival

proportion on that time point, but we can be able to estimate variance using the confidence interval by Parmar et al. (1998) method. This can be used to estimate the variance indirectly. If the $(1-\alpha)\%$ confidence interval is given for study i for each time point j, the variance can be estimated by:

$$var(S_{ij}) = \left[\frac{UpperCL_{ij} - LowerCL_{ij}}{2\phi^{-1}(1-\frac{\alpha_i}{2})}\right]^2 \tag{3.1}$$

where the $UpperCL_{ij}$ and $LowerCL_{ij}$ are the upper and lower limits of confidence interval for S_{ij} in study i on time point j, and $\phi^{-1}(1-\frac{\alpha_i}{2})$ is the cumulative standard normal distribution for a given α_i. Parmar et al. (1998) suggested that the confidence must be used in the level of significance figure to allow for reliable accuracy.

3.3.2 Univariate meta-analysis

Without loss of generality assume that the effect sizes of interest is approximately normal distributed. Let Y_i be the observed outcome in the i^{th} study. Where observations were done for each and every time point in the study (Parmar et al., 1998), $Y_i \sim N(\theta_i, \sigma_i^2)$, where the θ_i, denotes the mean and σ_i^2, denotes the variance in each of the studies, then a general linear mixed model for study i can be given as:

$$Y_i = \theta_i + \epsilon_i \tag{3.2}$$

where ϵ_i is the random error and is assumed to be independent and normal distributed $\epsilon_i \sim N(0, \sigma_i^2)$, where σ_i^2 is the variance (so that means it is assumed to be known) and Y_i is the effect size.

Fixed effect model meta-analysis

Under the assumption that all the factors that influence the survival proportion is the same in all studies and therefore the true effect is the same and can be denoted by θ, in this case, this can be modeled using the fixed effect model. It follows that the observed effect sizes vary from one study to the next only because of the random error inherent in each study and this is called within study variance (Borenstein et al., 2009; Larry & Ingram, 1985).

The fixed effect model has the assumption that there is a true effect θ that is common in all studies (Borenstein et al., 2009), the only thing that differs is the variance within each study. Generally the model is given as:

$$Y_i = \theta + \epsilon_i \tag{3.3}$$

where θ and ϵ_i are the true effect size and random error respectively. Let us assume that the observed effect sizes is normal distributed that is $Y_i \sim N(\theta, \sigma_i^2)$ since this is true $\epsilon_i \sim N(0, \sigma_i^2)$. It can be noted that even though the true underlying effect size is the same across the studies Y_i are not identically distributed because the random error variance are not the same across studies. The maximum likelihood parameter estimation of θ given σ_i^2 is based on the following likelihood equation (Normand, 1999; Pigott, 2012; Borenstein et al., 2009):

$$f(y_1, y_2, ...y_k|\theta, \sigma_i^2) = \prod_{i=1}^{k} \frac{1}{\sigma_i\sqrt{2\pi}} \exp\left\{-\frac{1}{2\sigma_i^2}(y_i - \theta)^2\right\} = L(\theta) \tag{3.4}$$

then the log likelihood can be written as:

$$l(\theta) = -\frac{k}{2}\log 2\pi - \sum_{i=1}^{k} \log \sigma_i^2 - \sum_{i=1}^{k} \frac{1}{2\sigma_i^2}(y_i - \theta)^2 \tag{3.5}$$

assuming the σ_i^2 known we will just only estimate the θ by maximizing log likelihood with respect to θ and get $\hat{\theta}$ as

$$\hat{\theta} = \frac{\sum_{i=1}^{k} W_i Y_i}{\sum_{i=1}^{k} W_i} \tag{3.6}$$

where W_i is the weight given by the inverse of the study variance in fixed effect meta-analysis that can be computed as:

$$W_i = \frac{1}{\hat{\sigma_i}^2} \tag{3.7}$$

where $\hat{\sigma_i}^2$ is the within study variance estimate for study i.
Thus $\hat{\theta}$ can be interpreted as a weight average of the effect sizes , and the variance of $\hat{\theta}$ given by:

$$\hat{V}(\hat{\theta}) = \frac{1}{\sum_{i=1}^{k} W_i} \tag{3.8}$$

Then the standard error (SE) is the square root of summary variance.

$$SE_{\hat{\theta}} = \sqrt{\hat{V}(\hat{\theta})} \tag{3.9}$$

The confidence interval (CI) of the summary effect can be estimated using equation 3.9 as the SE and a given level of significant value and is given by.

$$\hat{\theta} \pm \ z_{\frac{\alpha}{2}} \times SE_{\hat{\theta}} \tag{3.10}$$

where from the standard normal distribution we use the convention that $P(Z > z_a) = a$.
To test if the true effect sizes is zero, the Z-test is used

$$Z = \frac{\hat{\theta}}{SE_{\hat{\theta}}} \tag{3.11}$$

For one tailed the P-value is

$$P \ = \ 1 - \phi(z_\alpha) \tag{3.12}$$

and for two tailed test the P-value is

$$P \ = 2 \left(1 - \phi(z_{\frac{\alpha}{2}})\right) \tag{3.13}$$

where $\phi\,(z)$ is the standard normal cumulative distribution.

Random effect meta-analysis

In a random effects meta-analysis model, we assume there might be different underlying effect sizes across the studies (DerSimonian & Laird, 1986) which may cause the variation in the magnitude of the effect. It is assumed that the sample sizes are not infinite and that the mean sample error is not zero (Borenstein et al., 2009). Suppose the true effect for each study i is θ_i, then the observed effect sizes for each study will be less than or greater than θ_i.

If we assume the normal distribution curve, the distance between the overall mean and the observed effect sizes in any given study will consist of two distinct parts: the true variation in effect sizes (ξ_i) and the sampling error (ϵ_i). The observed effect sizes, Y_i, will be model as for any study given by the pooled mean, the variation of the study's true effect from the pooled mean and the variation of the study's observed effect sizes from the true effect sizes that is given as:

$$Y_i = \mu + \xi_i + \epsilon_i \tag{3.14}$$

The aim of the random effect meta-analysis is still on estimating the overall weighted mean and overall variance as we did in meta-analysis fixed effect model before. Where the weighted mean can be estimated using the similar technique as one in equation 3.6 the only difference will be that now we include the variation in between studies, that we can call τ^2. Then from this, there is a need of estimating the parameter of variance-between studies τ^2 using the methods of moments as proposed by DerSimonian & Laird (1986). It can be computed as follows: (in this study we will be using T^2 as the estimate of τ^2),

$$T^2 = \frac{Q - df}{C} \tag{3.15}$$

where,

$$Q = \sum_{i=1}^{k} W_i Y_i - \frac{\left(\sum_{i=1}^{k} W_i Y_i\right)^2}{\sum_{i=1}^{k} W_i} \tag{3.16}$$

and

$$df = k - 1,$$

where k, is the number of studies that will be included in the analysis, and C is given by:

$$C = \sum_{i=1}^{k} W_i - \frac{\sum_{i=1}^{k} W^2}{\sum_{i=1}^{k} W_i}. \tag{3.17}$$

This estimation comes from the fact that expectation of Q is given as:

$$E(Q) = (k-1) + (\sum_{i=1}^{k} W_i - \frac{\sum_{i=1}^{k} W^2}{\sum_{i=1}^{k} W_i})\tau^2 \tag{3.18}$$

and it gives the estimates of:

$$\hat{\tau}^2 = max\left(0, \frac{Q - (k-1)}{C}\right) \tag{3.19}$$

Then we can compute the summary mean effect sizes by first starting as to note that.

$$W_i^* = \frac{1}{v_i^*} \tag{3.20}$$

where

$$v_i^* = v_{y_i} + T^2 \tag{3.21}$$

and

$$\hat{\theta}^* = \frac{\sum_{i=1}^{k} W_i^* Y_i}{\sum_{i=1}^{k} W_i^*}. \tag{3.22}$$

Then the summary variance is the reciprocal of the sum of weights,

$$V_{\hat{\theta}^*} = \frac{1}{\sum_{i=1}^{k} W_i^*} \tag{3.23}$$

and the SE is the square root of equation 3.23

$$SE_{\hat{\theta}^*} = \sqrt{V_{\hat{\theta}^*}} \tag{3.24}$$

then the confidence interval may be computed as follows:

$$\hat{\theta}^* \pm \ z_{\frac{\alpha}{2}} \times SE_{\hat{\theta}^*}. \tag{3.25}$$

If we need to test the null hypothesis that say the mean effect is zero the z-test statistics is given by:

$$Z^* = \frac{\hat{\theta}^*}{SE_{\hat{\theta}^*}}. \tag{3.26}$$

The one tailed the P-value that is based on a specific significant level is

$$P^* \ = \ 1 - \phi\left(\pm |{z^*}_{\alpha}|\right) \tag{3.27}$$

and the two tailed test P-value is,

$$P^* = 2\left(1 - \phi\left(|z_{\alpha}^*|\right)\right) \tag{3.28}$$

where, $\phi(z)$ is the standard normal cumulative distribution.

3.3.3 Heterogeneity and dispersion proportion

The researchers should not only focus on knowing the summary of effect sizes, but it is also important to have information about the consistency and variation of effect sizes between the studies and consider the right method for that specific case (Borenstein et al., 2009). According to Cooper (2015) and Borenstein et al. (2009) the researchers suppose to ask the following questions when they analyse the meta-analysis study: Is there evidence of heterogeneity? How big is the variance between the studies? What is the real proportion of observed variation?

It is known that it is rarely case to have the same observed effect sizes; because of variation between studies there will be two causes of variation: heterogeneity of studies and random error (Borenstein et al., 2009). According to Borenstein et al. (2009); Pigott (2012) and Normand (1999) there are three steps to follow when dealing with the different sources of variability:

i)computing the total amount of study to study variation;

ii) to estimate how much the observed effect size would be expected to vary from each other if the true effect sizes was actually the same in all studies;

iii) the heterogeneity of studies.
The Q test statistic (Cochran Test) is used and it is sensitive to the ratio of the observed variance to the within-study error.

$$Q = \sum_{i=1}^{k} W_i(Y_i - \hat{\theta})^2 \tag{3.29}$$

where the W_i is the weight of study i, Y_i is the observe effect sizes of study i, $\hat{\theta}$ is the pool effect, and k is the number of studies included in the study. Equation 3.29 can be explained as the dispersion of each effect size from the pooled mean, then square it, weighted by the inverse-variance for each study i, and summing up all the studies to yield the weighted sum of squares (WSS), Q (Borenstein et al., 2009). It can be noted that metrics of effect sizes have no impact in Q.

If we need to know the expected value of Q, on the assumption that there is a true common effect (that means the studies share the common effect sizes) and the within study-variance is the only cause of variation in the studies. Since Q does not depend on metrics of effect sizes, the expected value depends on degree of freedom (df).

$$df = k - 1 \tag{3.30}$$

Now the study has observed Q (the total dispersion), and the expected Q or excess dispersion, also called the excess variation is given by.

$$Q - df \tag{3.31}$$

The next step is to test the assumption of homogeneity in effect sizes. The first question is whether there is any significant of heterogeneity in effect sizes, hence the statistic Q will be used to address the question. Under the null hypothesis that the meta-analyst will want to test is that the studies share a common effect size hence Q will follow central chi-square (chi^2) distribution with df, of $k-1$. So we can report a

$p-value$ for any observed Q values. Rejecting the null hypothesis at a given level of significance says 5% leads to the conclusion that the studies do not share a common effect size. The purpose of the test is to assess the variability of the null hypothesis and not to estimate the magnitude of the true dispersion (Borenstein et al., 2009; Normand, 1999).

According to (Borenstein et al., 2009) we can estimate τ^2 , the variance of between effect sizes using the DerSimonian & Laird (1986) (DL) Method. It is impossible to measure it directly, we can estimate it using observed effect sizes. To illustrate this, we start with the excess variation in equation 3.31 which represents the dispersion in actual effect sizes on a standardized scale; and we divide by quantity C, which is defined on equation 3.15 which has the effect of setting the ratio back to its original estimate and also making it an average rather than a sum of squared deviation. This means it resulting to statistics T^2 has the same metrics as the effect sizes, and it also shows the absolute amount of variation in that scale, if $T^2 = 0$, $Q < df$, but if $Q > df$ (it can be noted that T^2 cannot be negative) then if T^2 is positive and it is based on two factors: first is the amount of excess variation, and second the metrics of the effect sizes index. Note T is written in the scale of the effect sizes but T^2 is not. Like standard deviation in the primary study, the T can be used to show how the effect sizes distribution about the mean. We can conclude that T allows us to talk about the substantive importance of the dispersion about the mean effect sizes.

For the case of researching the proportion of the observed effect sizes reflecting the real difference in effect sizes, the researchers used I^2 statistics that was proposed by Higgins et al. (2003), to reflect this proportion, that could serve as a kind of signal-to-noise ratio,

$$I^2 = \left(\frac{Q - df}{Q}\right) \times 100\% \tag{3.32}$$

This is the ratio of excess variation to total dispersion. One can note that I^2 statistic is an explanatory statistics not an estimate of any quantity (Borenstein et al., 2009). Since I^2 shows the size of intersect of confidence intervals, which can be noted that does not show any exact location or outspread of the true effect sizes, it can be viewed as a measure of inconsistency across the findings of the studies and not as the measure of real variation across the underlying true effect size (Higgins et al., 2003; Borenstein et al., 2009). The I^2 index give us the idea of the amount of dispersion on a relative scale; we can say I^2 ranged from $0 - 100\%$ and it can be noted that if we get I^2 equal to negative percentage will put it as 0 that means there is nothing that can be explained with the observed heterogeneity as if I^2 is low, near-zero then there is nothing that can be explained about the studies variance; but if I^2

is high, then we can speculate about the reasons for the variance and also possibly apply a technique such as a subgroup analysis or meta-regression to try and explain it (Borenstein et al., 2009; Pigott, 2012). Higgins et al. (2003) provided benchmarks for I^2; they suggested values of the order of 25%, 50% and 75% as indicative of low, moderate and high variability respectively.

3.3.4 Computing the power in random effect meta-analysis for mean effect size

According to (Borenstein et al., 2009; Hedges & Pigott, 2001; Pigott, 2012) the power analysis can be computed using the following approach. An approximate significance test that the mean μ differs from a predefined constant μ_0 assuming the normal distribution when the null is true can be used. If the null is not true then Z^* the standardized statistics has a standard normal distribution with the mean

$$\lambda^* = \frac{\mu_. - \mu_0}{\sqrt{v^*_.}}, \tag{3.33}$$

and if the null is rejected the power of the one tailed test is given by

$$P = 1 - \phi\left(Z_\alpha - \lambda^*\right), \tag{3.34}$$

$\phi(x)$ is the standard normally cumulative distribution function.
The power of two tailed test can be computed, if the null is not true, which will happen if $|Z^*| > Z_{\frac{\alpha}{2}}$, which is similar to $Z^* > z_{\frac{\alpha}{2}}$ or if $Z^* < -z_{\frac{\alpha}{2}}$, then the power for the test case can be given as

$$P = 1 - \left(\phi\left(z_{\frac{\alpha}{2}} - \lambda^*\right) + \phi\left(-z_{\frac{\alpha}{2}} - \lambda^*\right)\right). \tag{3.35}$$

The equations 3.34 and 3.35 are not useful if the λ^* is not known, which depend on μ; the within study variance, v_i for $v_1,\ v_2, \ldots\ldots\ldots, v_k$ (we only assume that for all studies we have a common v (variance) (if v's are not the same Hedges & Pigott (2001) gives more details on how that issue must be handled) ; and between studies variance. As in homogeneity test in fixed effect case, if the within study variance is common we used the convention that was suggested by Schmidt & Hunter (1979). Hedges & Pigott (2001) proposed the approach when we dealing with heterogeneity, for small degree of heterogeneity $\tau^2 = 0.33v = \frac{v}{3}$ must be used , for medium degree $\tau^2 = 0.67v = \frac{2v}{3}$ must be used , and for lager degree $\tau^2 = v$ must be used. Then we can take all within study variance values as approximated to be common and

compute as:

$$v^*. = \frac{v + \tau^2}{k} \tag{3.36}$$

If the within study variance is not common, then the right hand side of equation 3.36 will be strictly larger than the left hand side of an identical within study variance. This will lead to underestimate of the statistical power.

There are several things that must be noted when performing the significance test, and power analysis test. The first is that the significance test is done when the study is already being collected and analysed; while the power analysis test is performed before the study analysis. It depends on a projected value rather than performed. Borenstein et al. (2009) mention that if the effect sizes is lower the power will be lower than the power of a larger effect sizes.

3.4 The publication bias

Publication bias occurs because in meta-analysis there is an inclusion criterion that the meta-analyst set out to be met but if it was not possible to do so, then there would be more chances of including studies with significant results (since there is more chance of publication of papers with significance result)(Egger et al., 1997; Sterne et al., 2004; Harbord et al., 2009). Ultimately this means the analysis will be biased against studies that were not published or the non-significant studies (since these studies will lack the chance of being included in the review analysis). Because we cannot be sure whether the meta-analysis is free of publication bias or not, an analyst needs to use the methods that can answer these questions: is there evidence of any bias? Is it doable that the whole impact is an unit of bias? and the way abundant of an effect may the bias have?

The problem might also be the small study effect which may lead to some studies not being published. Harbord et al. (2009) mention these three condition:

- the large studies are more likely to be published, where statistical significance has not been considered
- moderate-sized studies are at risk of being lost
- small studies have a high risk of being lost.

These three conditions show that publication bias is expected to increase as the sample size decreases.

A funnel plot can be used to test for any bias in the data especially publication bias. The funnel plot is a visual tool to aid in detecting publication bias in meta-analysis. Basically it is a scatter plot of the effect sizes (X-axis) from each study against the sample size or standard error (Y-axis) (Sterne et al., 2004). Visually, when the sample sizes are on the Y-axis, large studies appear toward the top of a graph and cluster around the mean effect size; while smaller studies appear at the bottom of a graph, thus the plot helps to identify how asymmetry the graph is. In the absence of publication bias, the funnel plot will be symmetric; and in the presence of publication bias the plot is expected to follow the model, with symmetry at the top,a few of studies missing within the middle and additional studies missing close to the lowest. If the direction of the effect sizes is towards the right, then near the bottom of the plot we expect a gap on the left where the non-significant of studies should have been if we had been able to locate them, also the converse direction is true (Sterne et al., 2004).

It can be noticed on the funnel plot that the source of asymmetry is not only bias but other sources of asymmetry can be the heterogeneity of effect sizes, data irregularities, artifact or chance (Egger et al., 1997; Sterne et al., 2004). In terms of heterogeneity, the meta-regression can be used to deal with that matter.

It is believed that small sample sizes cause overestimation of effect sizes (Harbord et al., 2009); might increase the type II error. So, for a meta-analysis contains which involves small studies, the results should be interpreted with caution, altogether with discussion and conclusion (Harbord et al., 2009; Egger et al., 1997).

3.5 Dependence of effect sizes between time points

If we know that in each of the included studies, effect sizes were observed over time for each time point, we are more interested in capturing the correlations between effect sizes within a study that are longitudinally observed or recorded. That can be done by modelling the correlation of serial of effect sizes within the study. Such data leads to the meta-analysis of longitudinal studies, which can be defined as the combination of effect sizes that were measured at pre-determined time points during the course of follow up (Ishak et al., 2007). In most cases, meta-analysis studies are reporting effect sizes that are reported at the same time point (for example from the time-origin, at 1 month, 12 months, and 24 months, etc) like in the case of Ishak et al. (2007) and Musekiwa et al. (2016)) and in many trials. If that is not the case there must be more consideration in terms of multiples parameters, since these are inherently correlated (Musekiwa et al., 2016).

There are pertain time points for some group of patients that are reported in each study over a period of time and there are correlations to be investigated, the effect of these time points. Arends (2006) and Ishak et al. (2007) stated that if these correlations are ignored, estimates can lead to an overestimated variance of the summary effect sizes and biased estimates. Some of the published authors avoid the correlation in different time points by carrying out a meta-analysis in each time point (Trikalinos & Olkin, 2012), but for more refined and unified analysis methods to handle correlated effect sizes in the meta-analysis have been developed and well-developed software to handle such cases are now available in much statistical software (Olkin & Gleser, 2009; Dear, 1994).

suppose there are k studies, denoted by $i = 1, 2, ..., k$ and T denotes the follow-up time. The data that we consider is time to event data. Let us say in study i there are T effects sizes recorded at times $t = 1, 2, ...T$, that are contained in an effect sizes T-dimensional vector $\mathbf{y_i} = (y_{i1}, y_{i2}, ..., y_{it}, ..., y_{iT})$. In survival analysis, the effect sizes are usually hazard ratios estimated at the T time points. Each y_{it} is estimated with a sample variance σ^2_{ij}, and the correlation between pairs outcomes (tt') within each study is $corr(y_{it}, y_{it'}) = \rho_{itt'}$. The approach is to extracts information that is used, by first estimating the vector $\mathbf{y_i}$ and corresponding variances of $\mathbf{S_i} = (\sigma^2_{i1}, \sigma^2_{i2}, ..., \sigma^2_{iT})$. As explained in the previous section, in a univariate meta-analysis approach, especially in the random effects model, the overall variation was within and between study variation. In a multivariate setting, the same partitioning of the variance holds where it not that different since now the overall variation is still between those two within and between study variation but in addition it also includes within and between study correlations (Mavridis & Salanti, 2013).

3.5.1 Models for outcomes in multiple time-points meta analysis

For the k studies, $i = 1, 2, ..., k$ that are observed at two time points each, we can estimate two (or more) effect sizes for each study. This means that for each study, i, the estimated effect sizes are $\mathbf{Y_i} = (Y_{i1}, Y_{i2})$ such that $\mathbf{Y_{it}} = x'_{it}\beta + z'_{it}\delta_i + \epsilon_{it}$, where x_{it} is a $l \times 1$ design vector for the l fixed effects. It correspond to β which is a $l \times 1$ vector co-efficients. z_{it} is a design vector, of dimension $q \times 1$, of a random effects δ_i. The effect ϵ_{it} is the residual term for the effect sizes $\mathbf{Y_{it}}$, the σ^2_{it} is the estimated of within study variance in time-point t. Let us consider a random effect model where the between study variance associated with effect size j is denoted by τ^2_j, which is the heterogeneity parameter for effect size j. The variance-co-variance structure is the sum of within and between study variation. The effect sizes are assumed to follow a multivariate normal (MVN) distribution as:

$$\begin{pmatrix} Y_{i_1} \\ Y_{i_2} \end{pmatrix} \backsim MVN \left(\begin{pmatrix} \mu_1 \\ \mu_2 \end{pmatrix}, \begin{bmatrix} \sigma_{i1}^2+\tau_1^2 & \rho_i\sigma_{i1}\sigma_{i2}+\rho_\tau\tau_1\tau_2 \\ \rho_i\sigma_{i1}\sigma_{i2}+\rho_\tau\tau_1\tau_2 & \sigma_{i2}^2+\tau_2^2 \end{bmatrix} \right) \tag{3.37}$$

The model can be written as the general linear mixed model (Laird & Ware, 1982),

$$\mathbf{Y_i} = \mathbf{X_i}\boldsymbol{\beta} + \mathbf{z_i}\boldsymbol{\delta_i} + \epsilon_i \tag{3.38}$$

where $\mathbf{X_i}$ is the $T\times(l)$ matrix with the observed covariates values for each of the studies and $\boldsymbol{\beta}$ the vector of l co-efficients, where the baseline is not included. Where $\mathbf{z_i}$ is a design matrix for the random effect of dimension $T \times q$ and $\boldsymbol{\delta_i}$ is a vector of a random effect associated with the study i. It is assumed that $\boldsymbol{\delta_i}$ follows an MVN distribution that is $\boldsymbol{\delta_i} \sim MVN(0, \boldsymbol{\Delta})$, where $\boldsymbol{\Delta}$ is the between study variance-covariance matrix involving the τ_i^2 and the unknown correlation parameter $\rho_{\tau(jj')})$ and the structure is given as:

$$\boldsymbol{\Delta} = \begin{pmatrix} \tau_1^2 & \cdots & \rho_{\tau(1,q)}\tau_1\tau_q \\ \vdots & \ddots & \vdots \\ \rho_{\tau(1,q)}\tau_1\tau_q & \cdots & \tau_q^2 \end{pmatrix} \tag{3.39}$$

and ϵ_i is a vector of random sampling errors associated with the study i which is independent of $\boldsymbol{\delta_i}$ and it is assumed to that $\epsilon_i \sim MVN(0, S_i)$. It can easily be shown that marginally $\mathbf{y_i} \sim MVN(\mathbf{X_i}\boldsymbol{\beta}, \mathbf{V})$ where $\mathbf{V} = \boldsymbol{\Delta} + \mathbf{S_i}$. It is noted that the structure of $\mathbf{V}$ may differ depending on the main interest of the model.

3.5.2 Fitting the multivariate meta-analysis

n this subsection, we are going to describe only the random effect model since the fixed effect is taken as a special case where the heterogeneity is equal to zero ($\boldsymbol{\Delta} = 0$) (Mavridis & Salanti, 2013). the main interest is on the effect sizes, the vector of summary effect for T outcomes (for simplicity let us make $\mathbf{X_i}\boldsymbol{\beta} = \boldsymbol{\mu}$) The focus of study interest is only on the random-effects model; the fixed effect model is taken as a special case where the heterogeneity is zero (Mavridis & Salanti, 2013). The main interest is on the effect sizes, the vector of the summary effects for the T outcomes (for this case lets us make $\mu = x_{it}\beta$; and the uncertainty which can be estimated by the $T \times T$ variance-covariance matrix $\mathbf{V}$ and $\boldsymbol{\Delta}$.

Likelihood

If we assume that all studies are independent experiments, as suggested by Mavridis & Salanti (2013), the log-likelihood to estimate the model parameter can be given as:

$$L \approx -\frac{1}{2}\Sigma_{i=1}^{n} log|\mathbf{\Delta}+\mathbf{S_i}| - \frac{1}{2}\Sigma_{i=1}^{n}\epsilon_i^{'}(\mathbf{\Delta}+\mathbf{S_i})^{-1}\epsilon_i$$

Then according to Ishak et al. (2007); Trikalinos & Olkin (2012); Mavridis & Salanti (2013) and Steel & Kammeyer-Mueller (2008) stated that this likelihood can be maximized by a numerical iteration methods using the expectation-maximization numerical, Newton-Raphson or Fisher scoring algorithms subject to restriction that $\mathbf{\Delta}$ is positive semi-definite. Although this method is good on estimating the estimates of interest, it can be computationally intensive and time demanding.

Maximum likelihood estimates

Assuming that all studies report the same outcomes and there are no missing values, then the summary estimates can be obtained by maximizing the likelihood:

$$\widehat{\boldsymbol{\mu}} = \left(\Sigma_{i=1}^{n}(\widehat{\mathbf{\Delta}}+\mathbf{S_i})^{-1}\right)^{-1}\left((\Sigma_{i=1}^{n}(\widehat{\mathbf{\Delta}}+\mathbf{S_i})^{-1})\mathbf{y}\right) \tag{3.40}$$

the summary estimates are approximately normally distributed with the variance-covariance matrix:

$$\widehat{\mathbf{V}} = (\Sigma_{i=1}^{n}(\widehat{\mathbf{\Delta}}+\mathbf{S_i})^{-1})^{-1} \tag{3.41}$$

The parameter $\boldsymbol{\mu}$ and $\mathbf{\Delta}$ are estimated iteratively in expectation-maximization numerically algorithm with equation 3.40 being one of the 2 steps. An approximation $(1-\alpha)100\%$ confidence interval can be obtained for $\widehat{\mu}_j$ as $\widehat{\mu}_j \pm z_{\frac{\alpha}{2}}\sqrt{\widehat{V}_{jj}}$, where $\widehat{V}_{jj}$ is the j-diagonal element of the $\widehat{\mathbf{V}}$ matrix. The alternative method that can be used is the quantile method based on the t-distribution (Mavridis & Salanti, 2013).

In case of missing outcomes 3.40 cannot be used directly to compute the estimates as the dimension of matrix $\mathbf{\Delta}$ and $\mathbf{S_i}$ will not be the same across studies (Mavridis & Salanti, 2013). This issue can be resolved by imputing those entries in the covariance matrix by allocating very large within-study variance to the missing outcomes and zero within-study correlation, ensuring that missing outcomes contribute negligible weight and information (Mavridis & Salanti, 2013; Trikalinos & Olkin, 2012) in the estimation of the combined effect sizes. Most of the difficulties will lie in the

estimation of between-study covariance matrix parameter $\mathbf{\Delta}$, which will be used in summary effect sizes estimation in equation 3.40.

In maximum likelihood estimation theory, the restricted maximum likelihood (REML) play an important role in producing unbiased estimate of variance and covariance parameter matrix in mixed models (Mavridis & Salanti, 2013). In fact REML has the capacity to deal with unbalanced data by design or that due to missing observations. In this case it can also be used to estimate the covariance matrix $\mathbf{\Delta}$ in the case of meta-analysis. The modified log-likelihood is given by:

$$RL \approx L - \frac{1}{2}\left|\sum_{i=1}^{n}(\widehat{\mathbf{\Delta}}+\mathbf{S_i})^{-1}\right| \tag{3.42}$$

Using Cholesky decomposition, $\mathbf{\Delta}$ can be ensured to be positive definite when maximizing the likelihood function, then to compute $\boldsymbol{\mu}$ and $\mathbf{V}$, $\widehat{\mathbf{\Delta}}$ can be used (Mavridis & Salanti, 2013).

Methods of moment

Method of moment estimation is another approach that can be used to estimate $\boldsymbol{\mu}$ and $\mathbf{V}$, for that reason the $\widehat{\boldsymbol{\mu}}$ and $\widehat{\mathbf{V}}$ will still be defined as in equation 3.40 and 3.41, but $\mathbf{\Delta}$ is estimated by employing a multivariate extension of the $Q \sim statistic$ and the method of moments was extended by Jackson et al. (2010) from DerSimonian & Laird (1986) method of moments

$$Q_j = \sum_{i=1}^{n} W_{ij}(Y_{ij} - \overline{Y_j})^2 \tag{3.43}$$

where $\overline{Y_j}$ is weighted mean of Y_{ij} across studies and the weights are

$$W_{ij} = \frac{1}{\sigma_{ij}^2}$$

Then on estimating the expectation, the Q_j that will include estimation of τ_j and μ_j is estimated as a weighted average with weights

$$W_{ij}^{*} = \frac{1}{\sigma_{ij}^2+\tau_j^2}.$$

When the multivariate approach will be similar to that of univariate. We can have p outcomes and $\mathbf{Q}$ is a matrix given by:

$$\mathbf{Q} = \begin{bmatrix} Q_{11} & ... & Q_{1p} \\ . & Q_{jj'} & . \\ Q_{p1} & ... & Q_{pq} \end{bmatrix} \tag{3.44}$$

where this element denotes $Q_{jj} = \sum_{i \epsilon N_{jj}} \frac{(Y_{ij} - \overline{Y_j})^2}{\sigma_{ij}^2}$ and $Q_{jj'} = \sum_{i \epsilon N_{jj'}} \frac{(Y_{ij} - \bar{Y}_{jj'})(Y_{ij} - \overline{Y}_{j'j})}{\sigma_{jj}\sigma_{jj'}}$. In this case N_{jj} denotes the set of studies where only outcome j is reported and $N_{jj'}$ is the set of studies where both outcomes j and j' are reported. $\overline{Y_j}$ is the weighted average of outcomes over the studies reporting only the outcome j (with the weights W_{ij} across studies) and $\overline{Y}_{j'j}$ is the weighted average of outcomes over the studies that report the outcomes of j and j' (with the weights $\sqrt{W_{ij}W_{ij'}}$ across studies). If there are missing values, they can be, handled by replacing them with arbitrary values with large within-study variance and summing all studies (Mavridis & Salanti, 2013; Jackson et al., 2010).

Jackson et al. (2010) show how to estimate $\mathbf{\Delta}$, by showing that it can be estimated by equating the expected value of $\mathbf{Q}$, $E(\mathbf{Q}) = \mathbf{E}$. It can be shown that the diagonal E_{jj} are function of σ_{ij} and τ_j, given as:

$$E_{(jj)} = E(Q_{(j,j)}) = (n_{ij} - 1) + \left(\frac{\sum_{i \epsilon N_{jj}} W_{ij} - \sum_{i \epsilon N_{jj}} W_{ij}^2}{\sum_{i \epsilon N_{jj}} W_{ij}} \right) \tau_j^2 \tag{3.45}$$

where n_{ij} is the number of studies included in the study, and $W_{ij} = \frac{1}{\sigma_{ij}^2}$. This is a linear function of unknown between study variance τ_j^2, hence by equating $E_{jj} = E(Q_{(jj)})$ and we can solve the linear equation to estimate τ_j^2 in a similar way as in univariate case. Off-diagonal elements $E_{jj'}$ are a function of $\sigma_{ij}, \sigma_{ij'}, \tau_j, \tau_{j'}, \rho_\tau$, which is given as:

$$E_{(jj')} = E_{(j'j)} = a + b\rho_\tau \tau_j \tau_{j'} \tag{3.46}$$

where

$$a = \Sigma_{i \epsilon N_{jj'}} \rho_i - \frac{\sum_{i \epsilon N_{jj'}} \frac{\rho_i}{\sigma_{ij}\sigma_{ij'}}}{\sum_{i \epsilon N_{jj'}} \frac{1}{\sigma_{ij}\sigma_{ij'}}} \tag{3.47}$$

,

$$b = \sum_{i \epsilon N_{jj'}} \frac{1}{\sigma_{ij}\sigma_{ij'}} - \frac{\sum_{i \epsilon N_{jj'}} \frac{1}{\sigma_{ij}^2 \sigma_{ij'}{}^2}}{\sum_{i \epsilon N_{jj'}} \frac{1}{\sigma_{ij}\sigma_{ij'}}} \tag{3.48}$$

. Additional $E_{(jj')} = E_{(j'j)}$ is a linear function of the between studies covariance $\rho_\tau \tau_j \tau_{j'}$, hence this can also be estimated from equation 3.46. Thus all the elements of $\mathbf{\Delta}$ can be estimated. However the method does not necessarily yield estimates of $\mathbf{\Delta}$ that are positive semi-definite. Jackson et al. (2010) give more details on how to handle that matter.

The advantage of this method is that there is no numerical maximization or iteration and because of that it saves time (Mavridis & Salanti, 2013). The other advantage is that the estimate of between study variance can be estimated without the assumption of normality (Jackson et al., 2010).

3.6 Meta analysis of survival curve

In the interest of doing pooling of survival time analysis methods using meta-analysis, there are some methods that were proposed. We look to a few of those that we think are essential for present work. Dear (1994) proposed the method which uses the fixed effects meta-analysis model using the iterative generalized least squares at multiple time-points(this method used the multivariate methods). In 1998 Parmar et al. (1998) gave a tutorial (basic approach on how to handle time to event meta-analysis) on how to extract the time to event data and showed how to analyse it. Arends et al. (2008) extended the Dear's methods to random-effect meta-analysis at multiple time points. It can be noted that most of these methods that had been proposed on dealing with the time to event meta-analysis have data that contain two arms of treatment.

For data that only has one arm treatment (single population), Combescure et al. (2014) proposed the method that can handle that. In this section we will briefly explain how it can be applied.

Let us start by explaining the basic method of survival probability, which is to use product limits estimator to analyze individual data. This is done by taking the survival probability at time t_j that is denoted by $S(t_j)$ as the product of conditional survival probability till interested time t_j (Collett, 2015), given as:

$$S(t_j) = p_1 p_2 \cdots p_j \tag{3.49}$$

where p_i for $i = 1, 2, ..., j$ is the probability that individuals was alive at time t_{i-1} and is still alive at time t_i.

Since in the current study there is a need for estimating survival probability, a similar approach as proposed by Combescure et al. (2014) will be used. To estimate the conditional survival probability we are going to use survival probability that will be extracted from published studies at each time point $(t_1, t_2, ..., t_J)$ for each study i. The conditional probability will be pooled using the common method in a meta-analysis that is the fixed-effect model and random effect model. Then the summary survival probability can be obtained by substituting the pooled estimates to equation 3.49 (Combescure et al., 2014; Jackson et al., 2010). Combescure et al. (2014) stated the advantage of using the Kaplan-Meier estimator is that the right-censored event is included in the estimates of p_i, thus also in the estimates of summary survival probability.

According to Combescure et al. (2014) let the extracted survival probability from published studies be denoted by $\hat{S_k}(t_j)$, where k represent the included studies and j range from 0 to J_K. Let the survival probability at the origin be 1 that is $(S_k(t_0) = 1)$. J_K depends on the length of follow-up in study k which vary across included studies. It will be like $J = max\{J_k\}$ which is taken as last time-point in the included studies. Let us assume the number at risk during interval $[t_{j-1}; t_j]$ is denoted by N_{kj} assuming they are all known in all included studies at time t_j. According to Combescure et al. (2014) the number of patients at risk before the first time-point is equal to number of patients included in study k (sample size). The number of patients at risk before the second time point can be computed as follows: number of patients at risk for (t_1, t_2) is equal to $N_k \times \hat{S_{k1}} = N_{k2}$, which generally can be calculated as $N_k \times \hat{S}_k(t_{j-1}) = N_{kj}$ (Parmar et al., 1998; Pocock et al., 2002; Williamson et al., 2002).

The conditional survival probability will be denoted by P_{kj} which is the probability that patients that were seizure free at time t_{j-1} in the study k are still seizure free at time t_j. P_{kj} can be computed as:

$$P_{kj} = \frac{\hat{S}_k(t_j)}{\hat{S}_k(t_{j-1})}, for j \geq 1 \tag{3.50}$$

Since by this approach we pool estimates using meta-analysis, this model assumed that the estimates are normally distributed or the number of studies are sufficiently large for central limit theorem. Then according to Combescure et al. (2014) there is a need of transforming probability before pooling it. The best transformation in this case is $arcsine$ with continuity of 0.25 (Anscombe, 1948; Brown et al., 2010; Rücker

et al., 2009). The $arcsine$ transformed probability is given by :

$$\hat{\pi}_{kj} = \arcsin\left(\sqrt{\frac{N_{kj}P_{kj} + 0.25}{N_{kj} + 0.5}}\right) \tag{3.51}$$

It is then assumed the $\hat{\pi_{kj}}$ is normally distributed with the variance of:

$$\widehat{Var}(\hat{\pi}_{kj}) = 0.25(N_{kj} + 0.5)^{-1} \tag{3.52}$$

It can be noted that the variance is estimated using the number of patients at risk at time t_j (if N_{kj} is large then a smaller variance than obtained when N_{kj} is small).

What can be noted for this correction method is that for a rare event or small sample size the normal approximation is not accurate. Since there is a vector of $\hat{\pi}_{kj}$ in study i, the vector can be denoted by $\hat{\boldsymbol{\pi}}_{\boldsymbol{kj}}$, and the covariance matrix of $\hat{\boldsymbol{\pi}}_{\boldsymbol{k}}$ can be denoted as $\mathbf{S_k}$, it can be noted that the $\mathbf{S_k}$ is diagonal since the conditional survival probabilities are not correlated and it should also be noted that the diagonal, within variance can be estimated using equation 3.51. When the summary estimates are also of interest these can be estimated using the random effect model. There will be a need to estimate the between-study covariance matrix which will be denoted by $\boldsymbol{\Delta}$. In the need of estimating the random effect model summary estimates the extended DerSimonian & Laird (1986) method that was proposed by Jackson et al. (2010) will play an important role. Since it is known that DerSimonian & Laird (1986) method are approximately normally distributed, the method that was discussed under subsection 3.5.2 can be used. To estimate $\hat{\boldsymbol{\pi}}$ and $\mathbf{V}(\hat{\boldsymbol{\pi}})$, equation 3.40 and equation 3.41 will be used too.

After this transformation is computed then the common method of pooling in meta-analysis will be applied to pool $\hat{\boldsymbol{\pi}}_{\boldsymbol{k}}$ and the confidence interval can be estimated, also the test of heterogeneity can be done like common meta-analysis method. After this method has been done the pooled conditional summary probability can be computed from pooled $\hat{\pi}$ using back-transformation:

$$\hat{P} = \sin^2(\hat{\pi}) \tag{3.53}$$

and the pooled survival probability is obtained by the product of conditional probability:

$$\hat{S}(t_j) = \Pi_{s=1}^{j}\hat{P}_s \tag{3.54}$$

where $j = 1, 2, ..., J$ denotes the time points, so we can use equation 3.52 to estimate summary survival probability up to time t_j and the confidence interval of time t_j

can be estimated by using delta method to get variance of pooled survival probability. To get the variance we must first transform $\hat{S}(t_j)$ using log transformation and $log(\hat{S}(t_j))$ is assumed normal distribution then using Greenwood formula by applying delta method (Collett (2015)) (the delta method by Combescure et al. (2014) is shown in Appendix 7.3).

3.7 Summary

This chapter generalized the meta-analysis methods of both fixed effect and random effect meta-analysis, when the interest is on using the univariate or the multivariate especially when the outcome of interest is measured over time (longitudinal meta-analysis studies).These methods will play an important role in the next chapter when we show how we combined the effect sizes of the studies that their interest was to model the time to seizure relapse.

Chapter 4

Systematic review

This chapter will show criteria that were used for the selection of studies, the extraction of the data from those published studies and software that can be used to meta-analyse the data.

4.1 Study selection

In this study, we used searched databases including the Google scholar, Medline and Pubmed which played a key role in guiding the study to the different online journals like ScienceDirect, Neurosurgery, Sage-pub, Brain, Epilepsia. We started searching for published studies without putting limits on the range of years, but it seemed that there were more studies conducted in recent years as medication and technology advanced compared to the past three decades where treatment was difficult. We then put the restriction from January 2000 to May 2017, a period of 17 years, since these were the times when more developments in surgery, especially of sensitive parts like the brain, became common (Ingram, 2013; Preul, 2005; Wickens, 2014).

The keywords that were important on searching for these published articles were: long term effect after epilepsy surgery, epilepsy longitudinal studies using the survival analysis, epilepsy surgery, neurosurgery, temporal surgery and survival analysis in seizure outcome after the epilepsy surgery.

4.1.1 Eligibility criteria

The eligibility criteria were:

1) Studies that were published from January 2000 to May 2017.

2) Articles based on quantitative research results and following this study design: cohort, case control and randomized controlled trial.

3) Articles published in English.

4) All studies had to be peer reviewed in academic journals.

5) Longitudinal studies: they must be followed-up (at least 1 year) after surgery and the analysis used survival statistics measurement (survival after surgery).

6) The study must be done on patients (human beings) that had gone for an epilepsy surgery treatment.

7) In those articles the classification methods of being seizure free (epilepsy) must be defined using the International League Against Epilepsy (ILAE) (Fisher et al., 2005; Wieser et al., 2001) and/or Engel Classification.

Engel classification is used to classify postoperative outcomes for epilepsy surgery. Engel (1993) proposed the Engel Epilepsy Surgery Outcome Scale, which has become the standard when reporting results in the medical literature. It is defined in four categories:

i) Engels class Ia is the first class; it consists of the patients who reported no seizure after their surgery.

ii) Engels class Ib is the second class; it includes both seizure free patients and those that experienced simple partial seizure or simple auras and neighbourhood seizure and drug withdrawal seizure.

iii) Engels class II it consists of patients that were not seizure free but had a substantial improvement, exhibiting only rare seizures.

iv) The forth subgroup, Engels III-IV, includes all patients with frequent seizures and a truly unsatisfactory outcome.

In most studies, these post surgery classifications were identified by the qualified neurologist and pathologist for each and every patient that was included in the study (Fong et al., 2011; **?**; McIntosh et al., 2004, 2012; Jeha et al., 2007; Berg et al., 2006; Sarkis et al., 2012; Bulacio et al., 2012; Jehi et al., 2009; Elsharkawy et al., 2008; Dupont et al., 2006; Ramesha et al., 2011; Paglioli et al., 2004; Bell et al., 2009; Mu et al., 2014; Garcia Gracia et al., 2015; **?**)

The interest in the current study was in finding the time to event (how long patients survive with seizure freedom after surgery), where event was seizure and time was the period after surgery (which in most of the studies was measured in months, if this was not true it was converted). Most included studies started with the preoperative patient evaluation, where an individual goes to electroencephalography (EEG) and Magnetic resonance imaging (MRI) for brain electrical activities and brain

lesion identification. Then after the surgery they did the post-operative evaluation, where they use MRI to take the internal brain image. Then after this, the neurologist, physicians and pathologist assessed each of the patients who were followed to check for seizure freedom. If the seizures had occurred, the time of the event (seizure) was recorded .

4.1.2 Search findings

As indicated in the flow chart in figure 4.1, this study only used the electronic search of available database which yielded 211 citations using the key search words. We carefully read the titles, abstracts and the studies that were not relevant were omitted. Then 84 studies were screened longitudinal studies where each patient was followed up over time. Thirty seven of them were excluded because they did not include the important points that were relevant for the study. The remaining 47 were important for the study because they had the follow up of at least one year; long term outcomes after epilepsy surgery were discussed; survival measurement was the outcome of interest. These 47 studies were screened again, where the focus was on the introduction, methods, and the results, respectively, to see if the primary studies include those important criteria and the important statistical outcomes. After that, only 16 studies remained that were included for meta-analysis. The essential point for the included studies was that the survival curve must be clear(survival proportion and time point). These 16 remaining studies were considered to be the best because they had a reasonable sample size, they used the survival analysis to calculate the seizure freedom (where their event of interest was first time to seizure recurrence post-operative). The focus was not that the survival proportion must be represented with the standard error but we were more concerned, about how many patients were at risk on particular time-points, then after that information was known, it was possible to compute variance for each survival proportion. The studies were done over time (longitudinal studies) at least one year of follow-up. In those studies, the surgery was done on humans and recently (between 2000 and 2017).

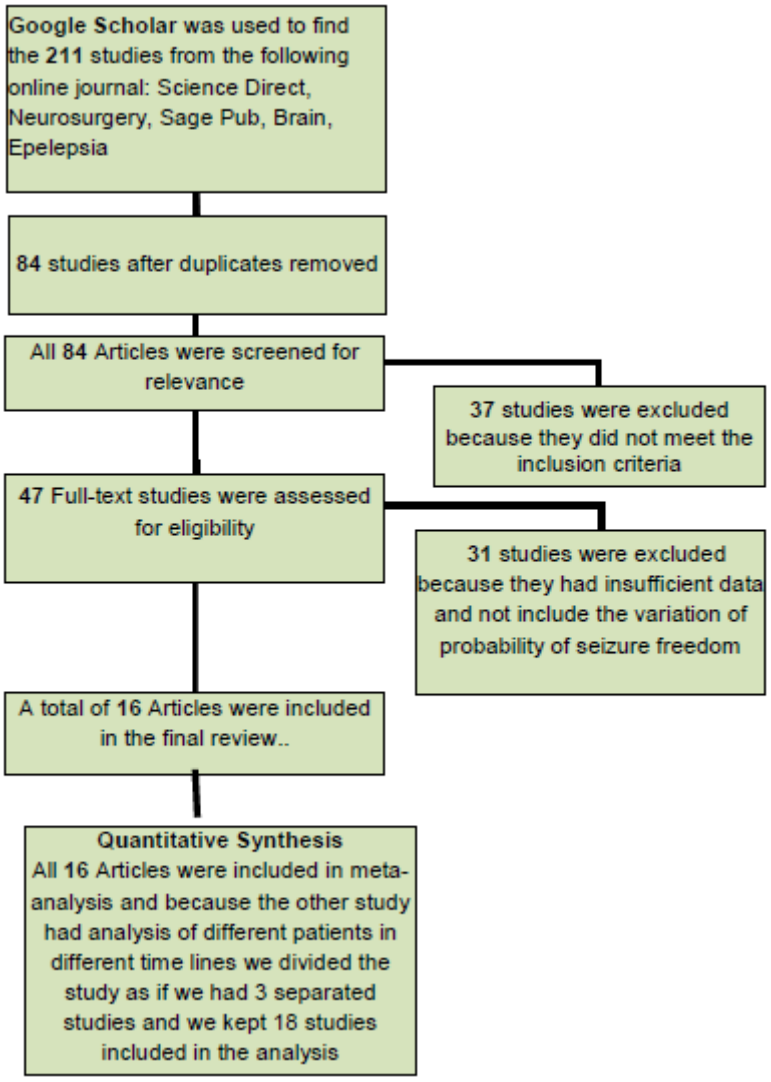

Figure 4.1 – A flow chart of the inclusion criteria

4.2 Summary of 16 studies (included)

Table 4.1 summarizes the information from 16 included the studies. It can be noted that the studies have varied years of inclusion (2000 to 2015). It can also be noted that most of those studies were done in developed countries (United State of America, Australia, United Kingdom, France and Germany) and few were from developing countries (1 in India and 2 from Brazil) which might give some problems in generalizing the result to the whole world.

Most of the included studies have a large sample which will be good for estimation. It can be noted that all included studies used survival analysis to analyze their

Table 4.1: Summary of included studies: Estimation of survival probabilty and the number of at risk patients in each time points

Study	Author	YearPub[a]	Location	6(S(R)[b])	12(S(R))	24(S(R))	36(S(R))	60(S(R))	120(S(R))	180(S(R))
1	Jei Mu et al	2014	Germany	0.74(46)	0.58(33)	0.55(26)	0.519(26)	0.479(23)		
2	Hemb et al	2012	Brazil	1.00(108)	0.88(108)	0.84(95)	0.82(92)	0.78(89)	0.69(85)	0.61(75)
3	Jeha et al	2007	USA	0.561(39)	0.557(22)	0.47(22)	0.451(19)	0.301(18)	0.301(11)	
4	Bell et al	2009	USA	0.72(44)	0.72(28)	0.66(24)	0.6(24)	0.6(24)		
5	Fong et al	2011	USA	0.801(64)	0.76(47)	0.65(33)	0.53(30)	0.47(11)		
6	Lowe e t al	2004	Australia	0.93(49)	0.82(48)	0.76(40)	0.7(33)	0.68(26)		
7	Paglioli et al	2004	Brazil	0.895(134)	0.85(120)	0.77(114)	0.7485(104)	0.74(101)	0.66(100)	
8	Ramesha et al	2011	India	0.967(492)	0.95(476)	0.875(468)	0.865(431)	0.741(426)	0.475(366)	
9	Mcintosh et al	2012	Australia	0.325(81)	0.235(27)	0.1885(20)	0.1701(16)	0.147(14)	0.127(12)	
10	Elsharkawy et al	2008	Germany	0.5(62)	0.492(32)	0.444(31)	0.444(28)	0.425(28)		
11	Elsharkawy et al	2008	Germany	0.571(52)	0.56(51)	0.538(49)	0.538(49)	0.535(46)		
12	Elsharkawy et al	2008	Germany	0.651(41)	0.629(39)	0.613(38)	0.613(38)	0.606(20)		
13	McIntosh et al	2004	Australia	0.674(325)	0.609(220)	0.553(198)	0.5(178)	0.477(163)	0.41(156)	
14	Bulacio et al	2012	USA	0.68(414)	0.61(282)	0.54(255)	0.47(224)	0.42(195)	0.33(174)	
15	Dupont et al	2006	France	0.976(110)	0.976(83)	0.852(73)	0.74(70)	0.595(34)	0.426(11)	
16	Grarcal et al	2015	USA	0.7985(466)	0.754(373)	0.675(352)	0.6459(315)	0.6395(301)	0.6(299)	
17	Jehi et al	2009	USA	0.731(57)	0.685(42)	0.658(40)	0.65(38)	0.548(38)		
18	Sarkis et al	2012	USA	0.71(63)	0.64(45)	0.585(41)	0.565(37)	0.52(36)	0.41(33)	

[a]YearPub=Year the study was published
[b]S=Survival Proportion and R= patients at risk

data, where Kaplan-Meier was used to calculate the proportion of seizure freedom over time and log-rank to compare survival proportion for different groups of interest. In studies that used multivariable analysis, their best option was the Cox proportional hazard model. To get the best variable that could be used in multivariate analysis, one of these methods was used: Wilcoxon rank test, Chi-square and Fisher's exact test and the significance of these variables being examined measured under 10% level of significance.

It seems that it will be difficult to do meta-analysis regression if heterogeneity is present in this study to explain the variation since there are different significant variables in each study. It can be noted that those studies that were done for surgery with normal MRI lesion have higher chances of survival (Fong et al., 2011) compared to not normal MRI lesional (McIntosh et al., 2004) when we ignore different timelines of studies. It can also be noted that those studies that were done on a patient with temporal lobe have higher chances of survival compare to others like frontal lobe or extratemporal lobe (Fong et al., 2011; McIntosh et al., 2004, 2012). The significant variables that appeared more than once were resection type, pre-operative or post-operative spiking (Bulacio et al., 2012; Sarkis et al., 2012; Jehi et al., 2009; Jeha et al., 2007). In some of the studies, there were no significant variables (McIntosh et al., 2004).

4.3 Data extraction

We are interested in the sample sizes of those included studies together with survival curve which help us to extract the survival proportion.

As it is indicated in Table 4.1 the number of patients in these studies ranged from 39-492. The follow-up time ranged from 6-180 months, but only one study had a follow-up that lasted for 180 months (Hemb et al., 2013). We only have 6-time points that were important for this study; 6, 12, 24, 36, 60, and 120 months. The reason for choosing these time-points were:

1 although it seemed that the post-operative check-up of patients were done monthly after surgery till 6 months, the 6 months seemed like an important time point to the authors because they only started presenting the results on this time point,

2 then the post-operative check-up was done yearly till 36 months.

3 After that, they did it after 24 months from 36 months of post-operative and at last after 120 months (that is 10 years).

Almost half of the studies end at 120 months of follow-up and the others ended at 60 months of follow-up.

It can be noted that there was no summary for 180 months since we cannot pool the result for only one study. Elsharkawy et al. (2008) had three separate groups that were done in different follow-up years (their main reason was to see, as time goes on, whether there were improving on how they performed the operation) also on different patients. The first group was followed from 1991 - 1995, the second group from 1996 - 2000, and the third group from 2001 - 2005. Only 5 studies show how many patients were at risk at particular time-points, especially the time points we were interested in (Bell et al., 2009; Fong et al., 2011; Lowe et al., 2004; Elsharkawy et al., 2008; Dupont et al., 2006). In the case where the number of at risk patients was not given at the time points, the following formula was suggested by Combescure et al. (2014) to determine at least patients:

$$N_{ij} = N_i S_{ij-1} \tag{4.1}$$

where N_i denoted the number of patients in the study i, S_{ij-1} denote the survival proportion in study i at time point t_{j-1} and N_{ij} is approximately the number of patients in study i at time t_j was used to calculate the number of risk patients at our interested time-points. If the study showed the number of patients censored between time point (t_{j-1}, t_j) then the number of risk patients would be subtracted like in the study of Mu et al. (2014).

The estimates of survival curves for the included studies can be observed in Figure 4.2. It is clear that the study by (McIntosh et al., 2012) had the smallest estimates across all time periods. Some studies had the survival estimates that do not start at $S_{ij}(0 = 1)$. This indicates that some surgical treatment were not so successful.

4.3.1 Statistical software

To analyse the meta-analysis data some standard statistical software can be used. In R the **RMETA** or **METAFOR** package can be used in SAS the **PROCMIXED** procedure, and in STATA, *metan* command can also be used. There are also software that were made to analyse the meta-analysis data only like Comprehensive Meta-Analysis (CMA) and RevMan to mention a few. To be specific, in this study, the R version 3.2.2 of 2015 by the R Foundation for Statistical Computing was used to analyse the data. The R software was chosen since it is freely available, it can be installed on a personal computer without a key license and if the required package is installed

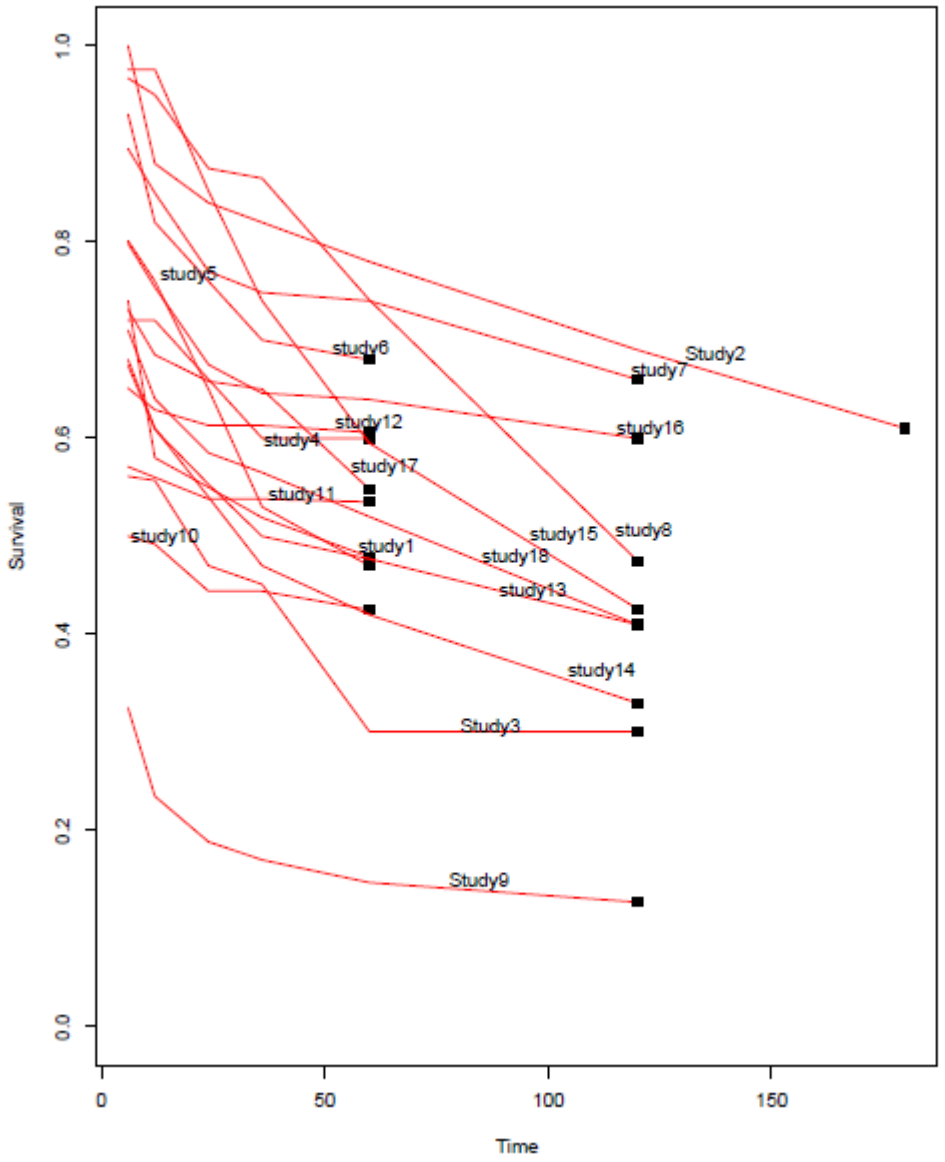

Figure 4.2 – Survival curve

it can be run without internet. The **RMETA** and **METAFOR** package, developed by Kovalchik (2013), will play an important role in modeling the data especially the fixed and random models (using different approaches Dersmonian and laird methods, likelihood or restrict likelihood estimator to estimate between studies variance (τ^2)). These packages will also play a key role in the graphical approach to model the funnel plot and forest plot which are important in interpreting the meta-analysis result.

Chapter 5

Univariate Analysis

In this chapter the univariate meta-analysis method was used to analyze the data that was shown in Table 4.1; here the meta-analysis coefficients at each time-point are modeled separately.

Since the assumption of the study was that we had included many studies, it was possible to use the central limit theorem; that means we assume that the summarized survival proportion is approximately normally distributed although we only have 18 studies. In the current application the survival proportion and variance of survival proportion were observed in each study i over 6 time-points that is after month 6, month 12, month 24, month 36, month 60 and month 120 (only 1 study, Hemb et al. (2013) followed-up to 180 months but it was not possible to pool it).

5.1 Fixed effect meta-analysis

The summary of survival proportion was computed for study i in each separate time-point (1, 2, 3, 4, 5 and 6). Our concern was only on the variation that was caused by the random error (that may be the fault in methodology or the way of collecting the data and so on in study i). All studies are assumed to have a common effect. Here, we assume the studies are independent.

5.1.1 Results

In total, there were 2647 participants who underwent epilepsy surgery. In those studies, the main focus was on the extratemporal lobe, temporal lobe and inferior frontal lobe as the types of epilepsy that the surgery treatment might be useful in treating. Since the interest of the study is the time to first seizure (relapse) post-operation, the study is interested in those studies that measured the time of relapse

using the survival analysis that has good properties of handling the time to event data. We observed survival proportion in a longitudinal term (survival proportion per each time point for a certain period), which are shown in Table 4.1. What is missing in Table 4.1 was only the variance per survival proportion which is useful when we amalgamated the outcomes of these studies but all the variances were included when the data was analysed. The study separated univariate meta-analyses at each time point using both fixed and random effect models. All were performed by **R**-software, using **metafor** package.

Univariate fixed effect model meta-analysis

Figure 5.1, shows the forest plot of univariate fixed-effect meta-analyses of survival proportion for seizure relapse after epilepsy for months 6, 12, 24, 36, 60 and 120 post-operative. The forest plot shows the survival proportion together with the corresponding 95% confidence interval (CI) for each study. The weight for each study is represented by the area of the box whose center also represents the size of effect sizes (survival) estimated from that study. The 95% confidence interval for effect sizes is represented by the horizontal bars. The length of horizontal bars is inversely proportional to the precision of the estimate for that study (that is, the shorter horizontal bar indicates more precisely the confidence interval, which is associated with the smaller standard error and large sample sizes). The overall survival proportion is shown by the middle of the diamond symbol whose left and right extremes represent the corresponding 95% confidence interval.

Table 5.1: Fixed effect summary

Time	SP[a](95% CI[b])	$(\chi^2 - p - value)$	No of studies	AIC
Month 6	0.78 (0.76, 0.80)	<0.0001	18	187.6024
Month 12	0.76 (0.74, 0.78)	<0.0001	18	137.6421
Month 24	0.70 (0.0.67, 0.72)	<0.0001	18	99.98
Month 36	0.66 (0.64, 0.69)	<0.0001	18	108.8651
Month 60	0.61 (0.59, 0.64)	<0.0001	18	56.8070
Month 120	0.50 (0.47, 0.53)	<0.0001	10	35.5992

[a]SP= survival proportion
[b]CI=confidence interval

Table 5.1 presents the results of the estimated summarized survival proportional that was analysed using the fixed effect model meta-analysis. The estimated survival at 6 months is 0.78, which means 78% of patients had not yet experienced a seizure

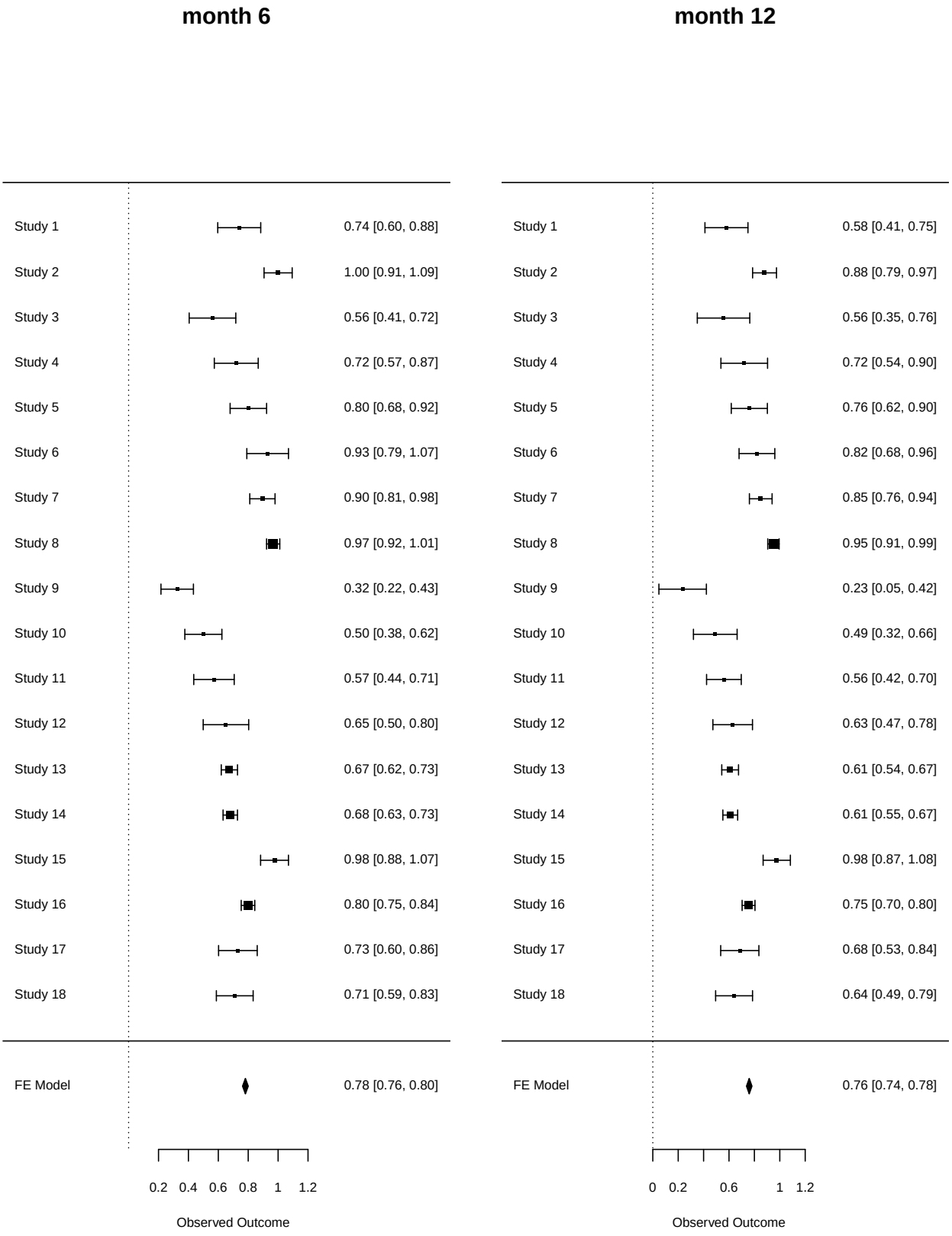

Figure 5.1 – Fixed effect forest plot for month 6 and month 12

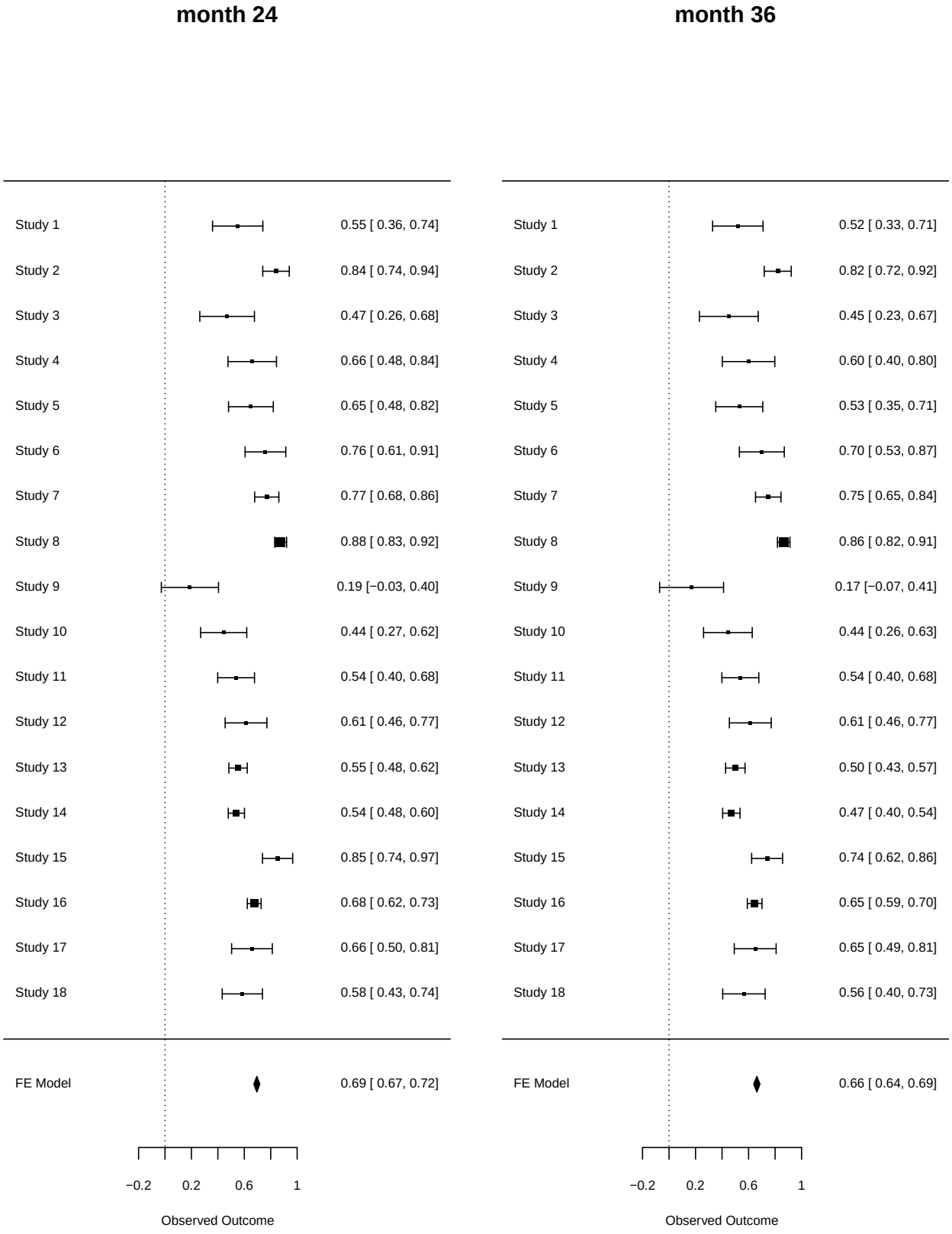

Figure 5.1 – Continued Fixed effect forest plot for month 24 and month 36

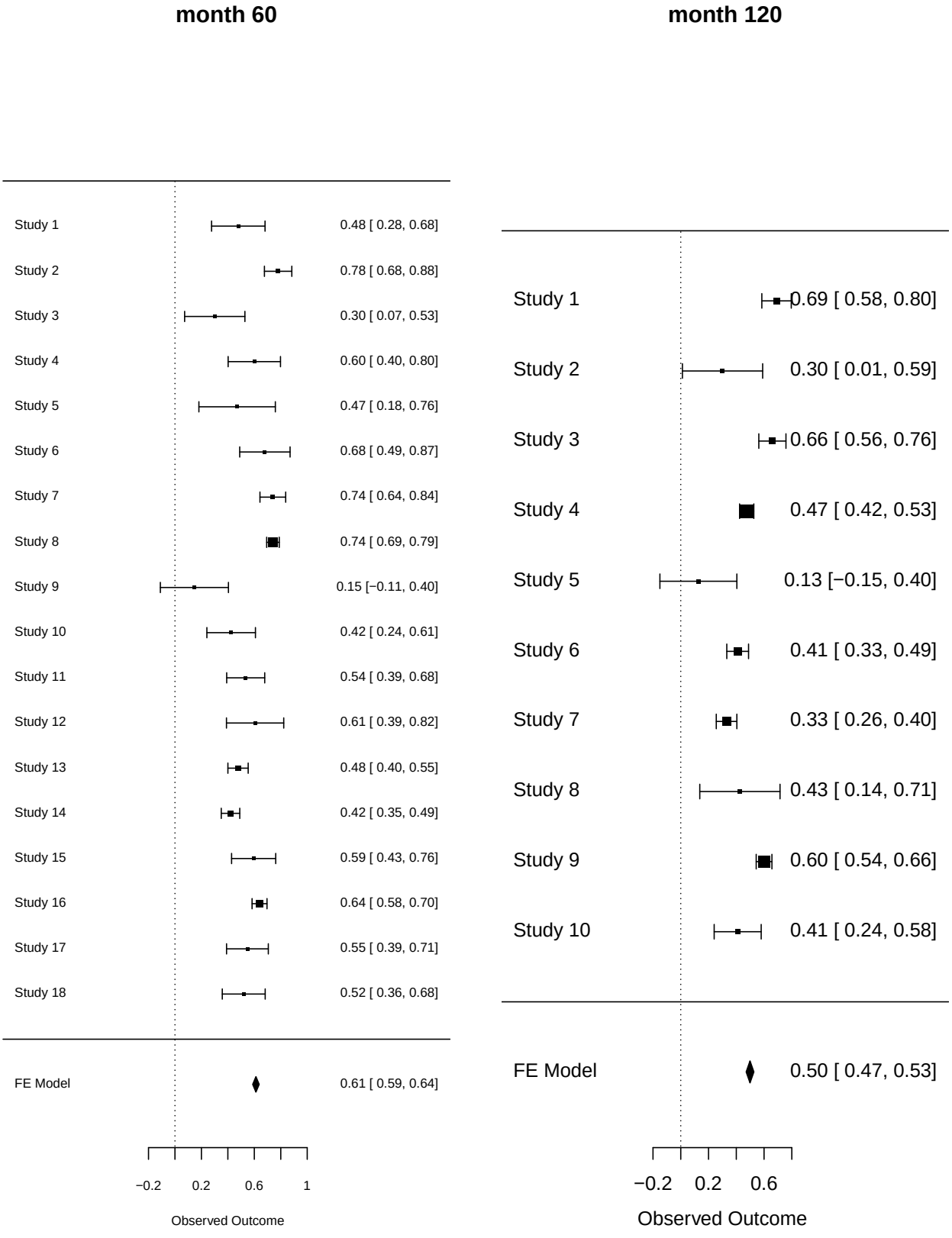

Figure 5.1 – Continued Fixed effect forest plot for month 60 and month 120

(seizure freedom) 6 months postoperative. The confidence interval tells us that we are 95% confident that the survival (seizure freedom) at month 6 ranges from 76% to 80%. At month 12, the pooled survival proportion tells us that 76% of patients were on seizure freedom and the confidence interval varies from 74% to 78%. The estimated pooled survival proportion is 0.7 after month 24 which implies that 70% of patients had not yet experienced seizure after epilepsy surgery, and we are 95% confident that the summarized survival proportion is between 0.67 and 0.72. After 36 months the estimated pooled survival proportion is 0.66 with a 0.64 to 0.69 confidence interval. After 60 months (5 years postoperative) the estimated summarized survival proportion is 0.61 with 95% confidence of 0.59 to 0.64 which means 61% of patients have not yet experienced seizure after surgery. The estimated survival after 10 years is 0.5 with 95% confidence interval of 0.47 to 0.53 (range of 0.6) which means after 10 years only half of the patients had not experienced seizure relapse after surgery.

The estimated pooled survival proportion was 0.78 at 6 months and decreased to 0.5 at 10 years (although there were 18 studies that were pooled for 6 months and only 10 studies for 10 years). That is, 28% patients experienced seizure after surgery between 6 months and 10 years. As was expected from the survival curve, it kept on decreasing over time (as seizure relapsing) and it can be noted that the decrease was large between 5 and 10 years, that is 9%.

The results suggest that heterogeneity was present in many time points that can be visually observed from Figures 5.1 by poor overlapping of confidence interval. It can also be noted that the study by McIntosh et al. (2012) had the worst proportion of seizure freedom.

5.2 Random effect meta-analysis

In this model, we computed the summary survival proportion to determine if there was any heterogeneity and the rate of variation between studies. In this model, the assumption of fixed population effect sizes was relaxed. As in the previous section, this model is still pooling the survival proportion at each time point separately.

We used the DerSimonian & Laird (1986) method for univariate random effect meta-analysis for each time point (post-operative months) utilizing the **R** software using DL method in *metafor* package. Figure 5.2 shows the forest plot of univariate random effect meta-analyses of survival proportion for seizure freedom post-operative for month 6, 12, 24, 36, 60 and 120 post-operative. Table 5.2 gives the

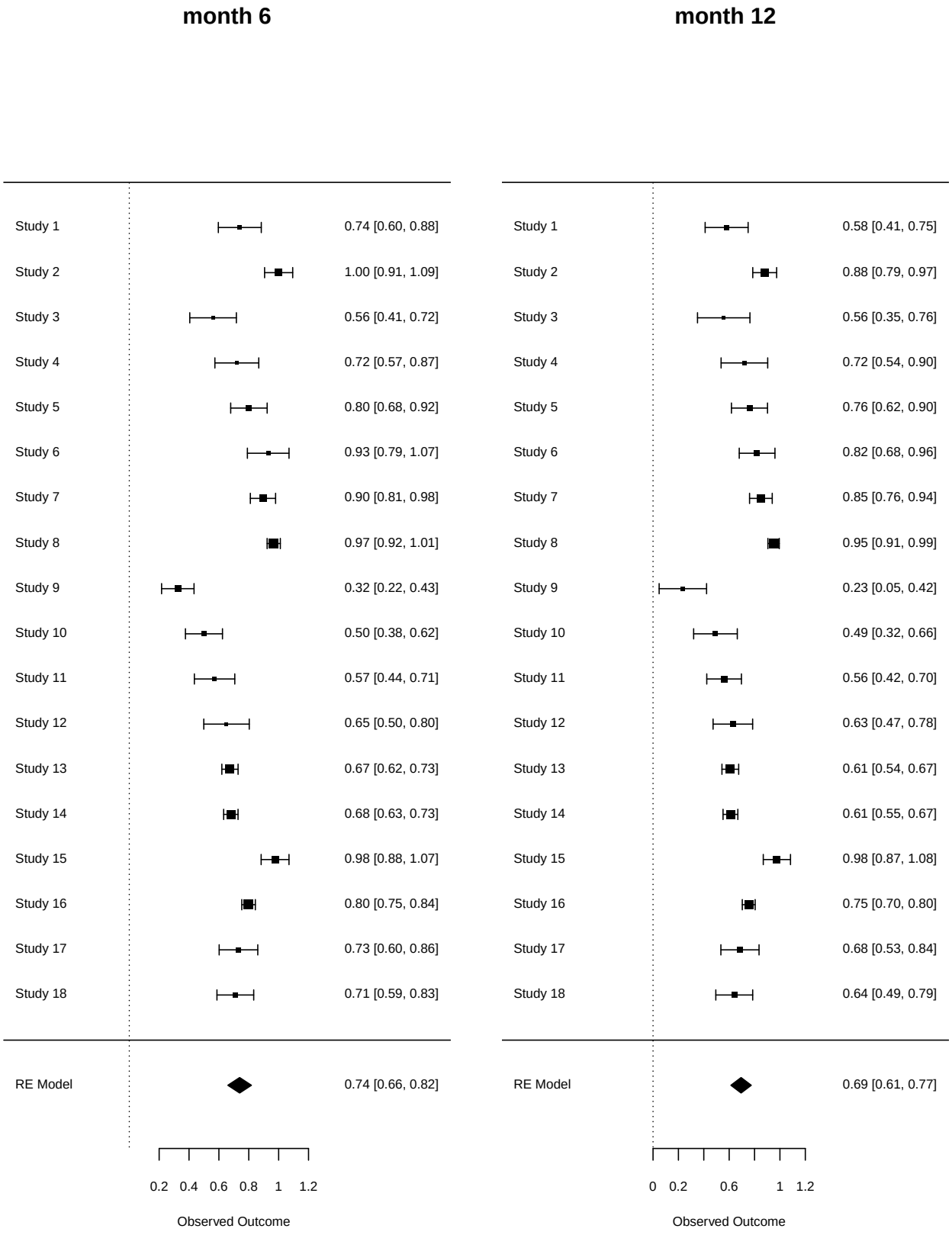

Figure 5.2 – Random effect forest plot for month 6 and month 12

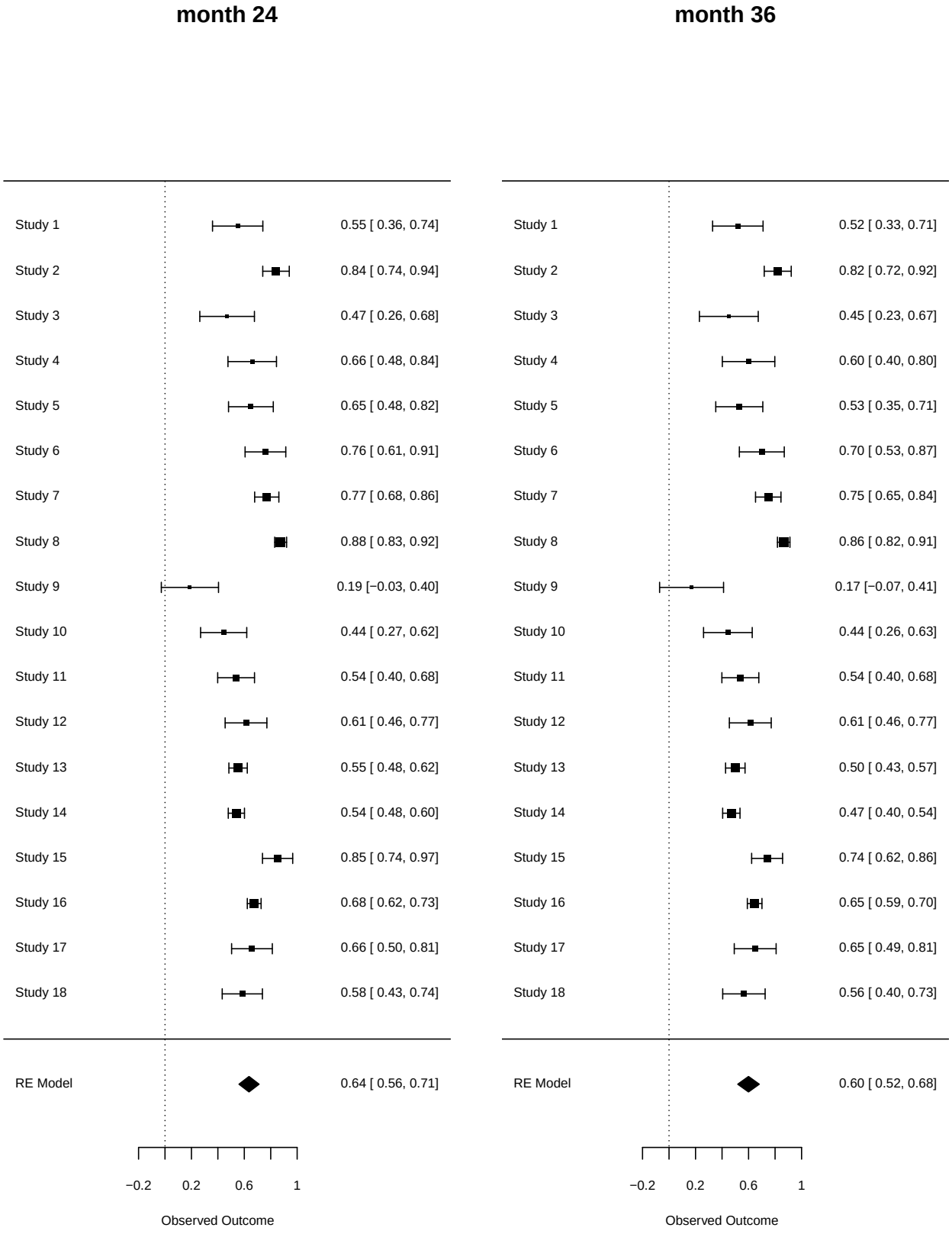

Figure 5.2 – Continued Random effect forest plot for month 24 and month 36

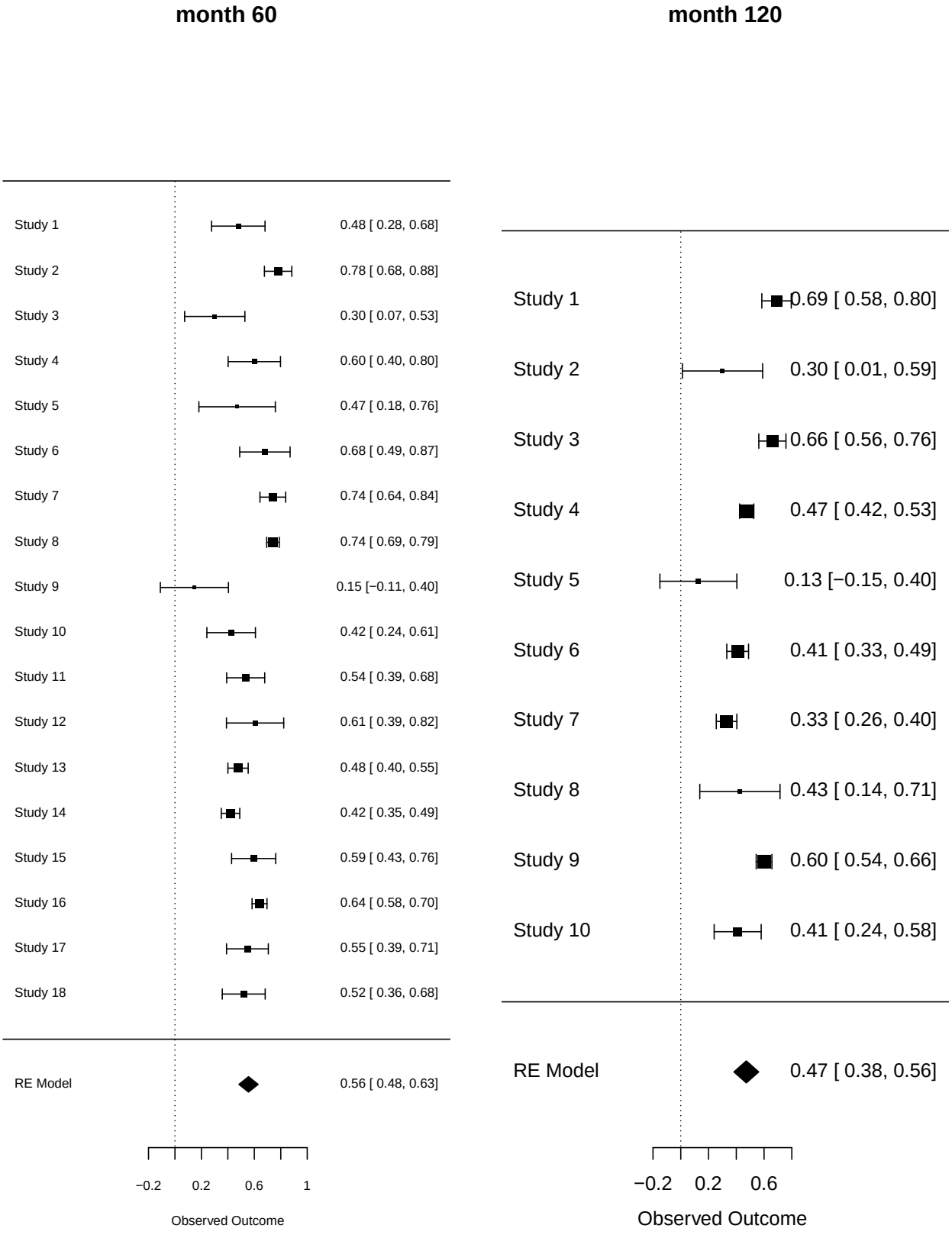

Figure 5.2 – Continued Random effect forest plot for month 60 and month 120

summary overall of random effect model meta-analysis, the outcomes of every time point, that is survival proportion and associated confidence interval, the heterogeneity p-value, and the value of heterogeneity not by chance (I^2).

The estimated pooled survival proportional at 6 months postoperative is 0.74 and 95% confidence interval of (0.66, 0.82), which means that according to random effect model there were 74 % of the patients who experienced seizure 6 months after surgery and we are 95% confident that survival proportion will vary from 66% to 82%. There exists 93.45% heterogeneity between studies. At 12 months postoperative it was estimated that there were 69% of patients who remained free from seizure after surgery, with a 0.61 to 0.77 95% confidence interval. The estimated survival proportion at 24 months is 0.64 which means 64% of patients achieved seizure freedom in this time interval and with 95% confidence the survival is expected to vary from 56% to 71%. At 36 months postoperative it was estimated that the survival proportion is 0.6 which means that 60% of patients were not yet experiencing seizure relapse after surgery, with 95% confidence that the survival proportion vary from 0.54 to 0.68. At 60 months (5 years) postoperative it was estimated that 56% of patients achieved seizure freedom, with 95% confidence that the seizure freedom is between 48% and 63%. At 120 months (10 years) the estimated survival proportion is 0.47.

It can be noted that the percentage of relapse from 6 months to 120 months postoperative was estimated to be 27%. It can also be noted that the survival rate kept on decreasing as the time passed (as expected from the survival time data of only one event expected to happen), and one can notice that between 60 months and 120 months, the estimated survival proportion decreased by 9% which is large between those time intervals that are displayed in the table. That may be because of the large interval of 5 years.

The τ^2 represent the estimation of variation between studies (between studies variance) using the DL method (we can also observe that in Table 5.2). One can notice that the largest estimate of τ^2 is at month 6, which means there were more variation between studies at this time point; as we observe from Figure 5.2 there is a poor overlapping of confidence interval. It can also be noted that the estimated value of τ^2 is smaller (that is 0.0153) in month 120. The reason for that might be caused by the few studies that are included in that month (less included studies that are 10 studies while the other time points had 18 studies) and it can be visually observed in the forest of month 120 plot (that is Figure 5.2) that there is some (not much because the heterogeneity is still present) overlapping of confidence interval.

Table 5.2: Random effect summary

Time	SP[a](95% CI[b])	χ^2 $(p-value)$	studies	τ^2	I$^{2c}(\%)$	AIC
Month 6	0.74 (0.66, 0.82)	<0.0001	18	0.0258	93.45	-7.4952
Month 12	0.69 (0.61, 0.77)	<0.0001	18	0.0255	91.64	-8.0692
Month 24	0.64 (0.56, 0.71)	<0.0001	18	0.022	89.68	-10.994
Month 36	0.60 (0.52, 0.68)	<0.0001	18	0.0253	90.11	-11.6189
Month 60	0.56 (0.48, 0.63)	<0.0001	18	0.01818	85.42	-12.9689
Month 120	0.47 (0.38, 0.56)	<0.0001	10	0.0153	87.31	-4.3749

[a]SP= survival proportion
[b]CI=confidence interval
[c]I^2=Statistics test of heterogeneity not by chance

The significance of heterogeneity between studies is present. This is shown in Table 5.2, column 3, all p-values are less than 0.05 and the I^2 (the estimation of heterogeneity of between studies not only by chance, that is estimation of true heterogeneity) test values are larger than 80% in all 6 time points.

5.3 Summary

This chapter analyzed the data using the univariate meta-analysis. What can be noted about this model is that it gives the summary of the survival proportion for each time-point. We can also note that the results are different from fixed and random effect model, the fixed effect has greater summary survival proportion values than a random effect. When we look at the measure of goodness of fit the fixed effect has the larger values of Akaike Information Criteria (AIC) compared to random effect model (the smaller the value the best the goodness of fit). That suggested that the random effect model was the best model to fit this data compare to the fixed effects effect model.

Chapter 6

Meta-survival analysis

In this chapter, survival analysis is used to meta analyse the data, that is random and fixed effect models.

6.1 Meta-Survival analysis in single-arm

There are 18 studies that are considered in this study, where study i has j (j=1,2,...,J) time points, where the survival probability was observed. What can be noted in this section is that we are not pooling the survival proportion at each time point separately (which we did in the previous chapter). This chapter uses the methodology that was discussed in section 3.6.

We computed the conditional probability for study i ($i = 1, 2, ..., 18$) for time point j (j=1,2,...,6), using the published survival probability of postoperative seizure freedom. Equation 3.50 was used to compute the conditional probability. Then the arcsine was used to transform conditional survival probability and it was corrected by 0.5. All this is well articulated in equation 3.51 and 3.52 and was used to compute the variance of conditional survival probability.

The transformed conditional probability for study i was taken as a vector for all j time-points, and its covariance matrix (that is diagonal since the conditional probability are not correlated and the diagonal variance was the variance for study i that was computed using equation 3.52). Then the conditional probabilities for all 18 studies were pooled using equation 3.40 also the covariance matrix of the pooled conditional probability was estimated using equation 3.41. This estimation was done for both fixed and random effects models. What can be noted is that the covariance matrix estimates has $\mathbf{\Delta} = 0$ for fixed effect model and for the random effect model the extended DerSimonian and Laird method was used to estimate $\mathbf{\Delta}$ (covariance

Table 6.1: Summary of random and fixed effect model: The transformed pooled conditional probability $\hat{\pi}$ and survival probability

		Fixed effect		Random Effect
Follow-up[a]	$\hat{\pi_i}^{FE}$[b] (SE[c])	$S(t)$ [95% CI[d]]	$\hat{\pi_i}^{RE}$[e] (SE)	$S(t)$ [95% CI]
6	1.1173(0.0097)	0.8081 (0.7932, 0.8232)	1.0636 (0.0544)	0.7655 (0.6808, 0.8613)
12	1.3308(0.00110)	0.7624 (0.7463, 0.7788)	1.3157(0.0270)	0.7140 (0.6246, 0.8163)
24	1.2640(0.0114)	0.6928 (0.6753, 0.7108)	1.2641(0.0121)	0.6462 (0.5614, 0.7438)
36	1.3529(0.0119)	0.6605 (0.6425, 0.6789)	1.3409 (0.0286)	0.6105 (0.5225, 0.7133)
60	1.3061(0.0125)	0.6153 (0.5967, 0.6344)	1.3013 (0.0347)	0.5700 (0.4892, 0.6641)
120	1.1322(0.0141	0.5043 (0.4845, 0.5250)	1.1613 (0.0574)	0.4755 (0.4078, 0.5545)

[a] Follow up in months
[b] Fixed effect
[c] Standard error
[d] Confidence interval
[e] Random effect

matrix estimates). Equation 3.53 was used to back pooled transformation conditional probability to get the conditional probability and then we used it on estimating the summary of survival probability the product-limit method (that is equation 3.54) used and the delta method was used to estimate the variance of the summary of survival probability. All this analysis was done using the **R** version 3.45. The package **MetaSurv** was used to analyze the data and to plot the estimated survival curve.

6.2 Results

The follow-up ranged from 6 months - 180 months and there was only one study that ended after 180 months. Our issue was that we can only pool two or more studies, hence our analysis ended at 120 months. It can be noted that the arcsine transformed conditional probability for study i at j time point (although this is not given in Table 6.1) was the lowest for the lowest number of patients at risk, while the variance of the transformed conditional probability was higher. The pooled arcsine transformed conditional survival probability and standard error is given for both random and fixed model in Table 6.1.

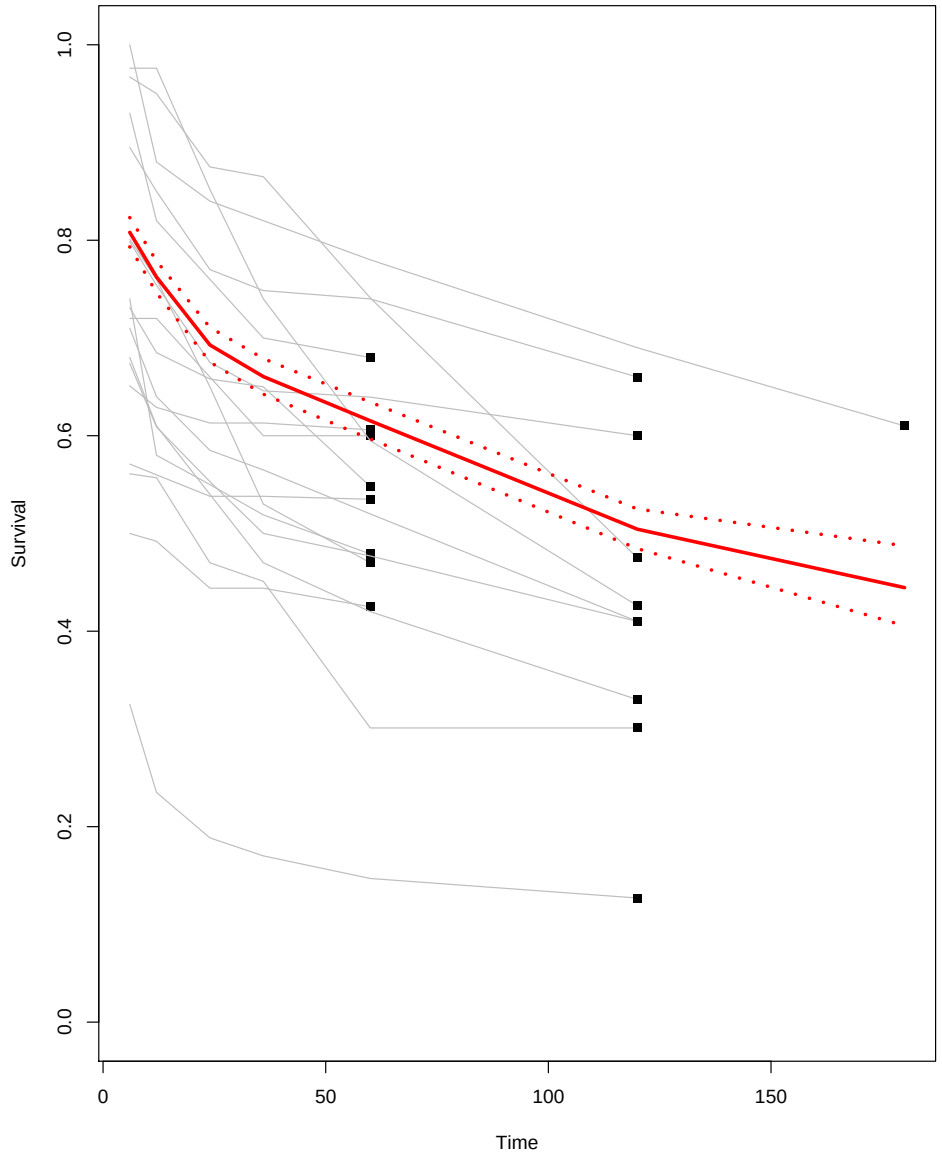

Figure 6.1 – Survival curves of the overall seizure freedom for the postoperative patients in the 18 studies of meta-analysis. The grey lines represent the survival in each study and the black square is the end of follow-up. The thick red line the summarized survival curve of seizure freedom with a 95% confidence interval(dashed red line) Obtained using the *MetaSurv* with **fixed effect**

Table 6.1 gives the results of the pooled conditional probability and the standard error for every time point (that is π_i and the $S.E(\pi_i.)$ for both the fixed effect model and the random effect model, and it also gives the results of summarized survival probability for both fixed and random effect models.

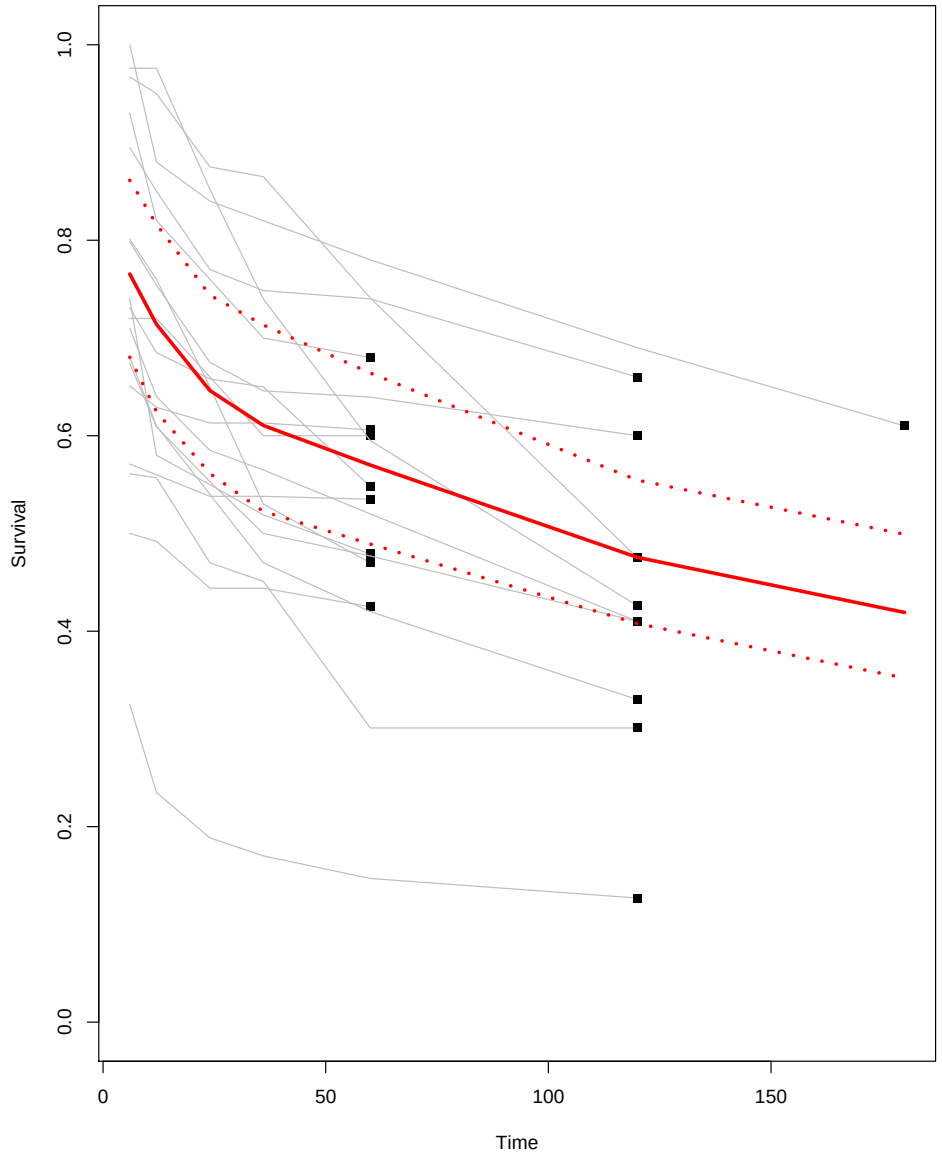

Figure 6.2 – Survival curves of the overall seizure freedom for the postoperative patients in the 18 studies of meta-analysis. The grey lines represent the survival in each study and the black square is the end of follow-up. The thick red line represent the summarized survival curve of seizure freedom with a 95% confidence interval (dashed red line) obtained using the *MetaSurv* with **random effect**

The estimated π_i for the fixed effect model are large for time point 36 months which indicates that there were large conditional probabilities in this time point. There is a small standard error in month 12 which indicates there was large number of patients at risk at this time point, while as expected, at 120 months of follow

up, the standard error is larger than the other 5 time points, since they were fewer patients at risk at that time point. One can notice the increase of the standard error which indicates a decreasing number of patients at risk of seizure relapse with time period increased (which indicates that most patients have already had seizure relapse).

Also in Table 6.1, the estimated π_i for the random effect model is large at 36 months of follow-up and the standard error at 120 months time points which might be the result of large random effect in these time points. The estimated π_i are similar for 4 time points except for 6 months of follow up and 120 months of follow- up; this can be well explained by the weight allocated on that time- points (using the variance).

Also in Table 6.1, the summary of survival probability estimation is given, together with their 95% confidence interval that was obtained using the extension of Greenwoods formula, for both fixed and random effect model.

The summarized survival probability estimation in fixed effect model at 6 months of follow up is 0.8081, which means that 80.81% patients had not yet experienced seizure relapse 6 months post-operative, and we are 95% confident that the summary survival will vary from 79.32% to 82.32%. At 12 months of follow-up the estimated summary of survival probability was 0.7624, which means 76.24% of patients achieved seizure freedom after 12 months postoperative and we are 95% confidence that the summarized survival probability will vary from 74.63% to 77.88%. The summary survival probability was estimated to be 0.6928 at 24 months postoperative with 95% confidence interval of 0.6753 to 0.7108. At 36 months of follow- up the estimated survival probability is found to be 0.6605, which means that 66.05 % of patients have not yet experienced seizure relapse 36 months postoperative, with 95% confidence that the summarize survival probability will vary from 64.25% to 67.89%. The estimated summary survival probability was found to be 0.6153 at 60 months post-operative and with 95% confidence that the summary survival probability will vary from 0.5967 to 0.6344. At 120 months (10 years) of follow up the estimated summarized survival probability is 0.5043, which means 50.43% of patients were seizure free at 10 years postoperative, with a 95% confidence that the summarized survival probability varies from 48.45% to 52.50%.

Figure 6.1 gives the estimated fixed effects survival curves (which are plotted in grey) from the 18 published studies. By observing the graph, one can notice inconsistent seizure freedom (from different published studies) because they are spread all over the graphs over time. The estimated summarized survival probability is

plotted in red, while the 95% confidence interval is plotted in dashed red, which is narrow and that might suggest that the standard error of this model is small. From the red plotted curve, one can notice that at 6 months of postoperative, the seizure freedom was 80%. This means that about 20% of patients who underwent operations have already experienced seizure relapse in a short time of 6 months. One can also notice that the median of seizure freedom is slightly greater than 120 months (10 years) of postoperative.

Table 6.1 also gives the estimation of the random effect model. At 6 months of follow up the summary survival probability estimation is 0.7665 with a 95% confidence interval of 0.6808 and 0.8613, which means that 76.65% of patients had not yet experienced seizure relapse 6 months postoperative with 95% confidence that the summary varied form 68.08% to 86.13%. The estimated summary survival probability estimation at 12 months of follow up is 0.7140, which means that 71.4% of patients were still seizure free at 12 months postoperative. At 24 months of postoperative the estimated summary of seizure probability is 0.6462 and the confidence interval 0.5614 and 0.7438, which can be interpreted to indicate that 64.62% of patients were seizure free at 24 months postoperative with 95% confidence that summary of seizure probability will vary from 56.14 % to 74.38%. The estimated summary of survival probability is 0.6105 at 36 months of follow up with a 95% confidence interval of 0.5225 to 0.7133. At 60 months (5 years) of follow up, the estimated summarized survival probability is 0.57, with a 95% confidence interval of 0.4892 to 0.6641, which means 57% of patients were still free from seizure relapse 60 months postoperative with a 95% confidence that the summarized survival probability is from 48.92% to 66.41%. At 120 months (10 years) of follow up the estimated summarized survival probability is 0.4755, which means that 47.55% of patients were still on seizure freedom at 120 months postoperative.

Figure 6.2 gives the estimated random effects survival curves (that estimates the seizure freedom over time) that are plotted in grey for all 18 included studies. The estimated summarized survival probability is plotted in red, while the 95% confidence interval is plotted in dashed red. The 95% confidence interval is wider than that of the fixed effect model, which might be an indication of a large standard error (which might be true since the survival curves of the published studies are all over the graph. This might be an indication of variation between the studies that means the heterogeneity is present. From the red plotted curve, one can notice that at 6 months of postoperative the seizure freedom was approximately 77%, which means about 23% (if we ignore the censored patients) of patients who underwent the operation have have already experienced a seizure relapse in a short time of 6 months.

One can also notice that the median seizure freedom time is less than 120 months (10 years) of postoperative.

Heterogeneity was present, since the value of heterogeneity statistics is $Q = 880.7$ and was significant and the $I^2 = 90.58\%$. This confirms that the random effect approach is reasonable for this data. The result of the median survival time was found to be 104.46 months (almost 9 years) using the random effect model. These were found in the analysis using **R** statistical software. Although it is not given in the Table, we will show how to estimate it in Appendix 7.3.

The summary survival estimates of the fixed effect model are systematically larger than the summary survival estimates of the random effect model. The presence of random effect increase the variance of the published survival estimates, which that may be the reason of the confidence interval of random effects to be wider than that of the fixed effects.

Chapter 7

Discussion and Conclusion

Epilepsy affects 1% of the younger age population and 3% of the older age population, regardless of gender or race (Browne & Holmes, 2008). It can be estimated that there might be some increase of proportion if there were also more studies in developing world that focused on it (Hirtz et al., 2007; Seneneyake & Román, 1993; Newton & Garcia, 2012; Birbeck et al., 2002). Although it increases the risk of death by 1.6 to 4.1 (standardized mortality ratio) of the general population, it is a controllable disease (Hitiris et al., 2007), (Shorvon et al., 2015b). The concern with epilepsy patients are those patients with parmacoresistante epilepsy, which is been found to be costly, especially when medical treatment is being used to diagnosed condition of patients, while there is no seizure freedom is being achieved (Forsgren et al., 2005),(that threatens the quality of life in an individual).

One suggested option for drug resistant patients is surgical treatment. Successful surgery treatment has increase from 1986 to 1999 from 43% to 85% (Panel, 1990; Engel Jr et al., 2003; Engel Jr, 1993). In a paper by Engel Jr et al. (2003), the proportion of achieving seizure freedom after the epilepsy surgery was 63.2% with a 95% confidence interval of (60%; 66%). This was a result of short term outcome (less than 5 years) of seizure after epilepsy surgery. In 2005 Téllez-Zenteno et al. (2005) was concerned with the long term outcome of seizure after epilepsy surgery, then they did the review of the studies that were done for 5 years or more and their pooled outcome proportion was 66% with a 95% confidence interval (62, 70) of patients who achieve seizure freedom in temporal lobe. These studies show some good clinical results on achievement of seizure freedom on patients, but the concern was that some of the studies in Téllez-Zenteno et al. (2005) just give the proportion at the end of follow-up without giving the proportion within the follow-up (lack of using the survival analysis methods which have some advantage on that).

In this study, we had 18 studies which include study that had 3 trials with different patients and different times. The 18 studies were observed at 6 time points (6, 12, 24, 36 ,60 and 120 post-operative months). The survival on seizure was observed at these time points.

Univariate analysis was performed by pooling the proportion of seizure freedom in separate time points (months 6, months 12, months 24, months 36, months 60 and months 120). Since the AIC of random effect was less than that of fixed effect model (that is for fixed effect model greater than 35, while for random effect less than -4) the random effect model was the best model of analyzing our data, and the summary proportion of seizure freedom keep on decreasing with time. Although the surgical treatments can be regarded as the best treatment in refractory epilepsy, some patients experience seizure relapse (Téllez-Zenteno et al., 2005). Most of the included studies have high seizure freedom soon after the surgery (within 5 years)(except (McIntosh et al., 2012; Elsharkawy et al., 2008).

The non-parametric method to analyze the survival probability in studies that have only single arm treatment that was proposed by Combescure et al. (2014) was used to pool the quantitative data. This is the right method to summarize the survival estimator from the aggregate data (result from published articles) to model the fixed and random effect model. To compare this method with the separated time point analysis, it has some of these advantages: the pooled survival probability at time t involves all the results of the studies ending before this particular time-point, which that may enlarge the 95% confidence interval. It also gives the variation between studies in the same time-point and also between time-points.

It was the right decision to use it since time to seizure relapse is not a rare event which was going to the underestimate the proportion of seizure freedom if that was the case. In many studies, the number of patients at risk was reported. If that was not the case, it was calculated, since this methods required to give accurate variation to weight the conditional survival probability.

There was no method used to compare the fixed and random effect model in multivariate analysis. However, since the true heterogeneity between studies percentage is high, it was decided to only discuss the results from the random effect model. Based on the results, there was a bigger proportion of seizure relapse 6 months post-operative. Since the seizure freedom proportion is 0.7655 which means that about 23% of patients had already experienced seizures 6 months after surgery. This is quite a big proportion of patients who failed in such a short period. This might

be the result of incomplete epilepsy surgery because of many seizure relapses that occur immediately after surgery. The reason of early seizure relapse post-operative surgery might be: new seizure foci developed (Wieser & Hane, 2003), the frontal lobe has a large size which that might be the cause of incomplete surgery (Téllez-Zenteno et al., 2005). Overall from all the studies, survival after surgery is substantially low.

7.1 Limitations

Deciding on the inclusion criteria was a challenge. Some studies were based on the common studies that were dealing with the long-term seizure outcomes (Téllez-Zenteno et al., 2005; Toninia et al., 2004), some were based on the strategy of how to deal with the longitudinal data (Ishak et al., 2007; Musekiwa et al., 2016), and some on how to analyze meta-analysis survival time data (Arends, 2006; Taghavi, 2014; Combescure et al., 2014). Our study time points were also based on the included studies, that had the large interval between two time points especially month 36 and month 60 (interval period of 2 years); and the interval between month 60 and month 120. This can result in underrate proportion between these time points.

This thesis was more concerned with only surgical treatment (only resective surgery studies), but to also perform meta-analysis of studies that compare the survival per time of patients between two arm (surgery and medicine) might be of interest. There is also one known random clinical trials studies that compared the surgery and medicine, to increase those studies may increase the clinical solution to the drug resistance patients. To use two arms studies will be a better option of using the parameter estimation method that suggested by Arends (2006) in random effect model meta-analysis and the co-variance structure that was used in Musekiwa et al. (2016) studies to know the correlation proportion between two time points.

7.2 Area of future research

This study only focused on one effect size, survival ($S(t)$). It is also important to analyze other effect sizes in one study. Therefore the model can be extended to be able to incorporate multiple effect sizes. Secondly, since missing data is one of the common problems in longitudinal studies, it is also important to address and incorporate advanced missing data techniques in the case where some studies have missing observations at particular time points.

7.3 Conclusion

This study performed a systematic review to come up with studies that performed survival analysis on epilepsy after a surgery. Eighteen studies fitted in the inclusion criteria from these we found that about 50% of the patients who undergo the treatment will relapse within 10 years. It is, therefore, advised that clinicians may continue looking for more and efficient treatment methods that have a life- long successful treatment. Meta-analysis has proved to be a good approach in amalgamating all the findings from all over the world.

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Appendix A

A.1 Summary survival rate variance

We taken the idea of individual data, where we get the variance of the survival rate of non-parametric estimation, using the Greenwood formula, by delta method application. Using the Combescure et al. (2014) proposal to get the variance of pooled survival rate. Let us assume we have $(t_1, t_2, ...t_J)$ then we logarithm equation 3.54, then we apply the delta method to get the variance of logarithm of pooled survival rate. For simplicity let us start by getting the scalar variance of the pooled survival rate, we know that the delta method is given as:

$$var(f(x)) \approx (f^{'}(E(x)))^2 var(x) \tag{7.1}$$

which in our case it derived to be:

$$var(\log(S(\hat{t}_j))) = 4\sum_{s=1}^{j} \frac{var(\hat{\pi_s})}{\tan^2(\hat{\pi_s})} \tag{7.2}$$

If we derive equation for covariance matrix case, derive it using the the pooled $\hat{\boldsymbol{\pi}}$ we get:

$$var(\log(S(\hat{t}_j))) = 4\sum_{u\leq j}\sum_{v\leq j}\left[\frac{cov(\hat{\pi_u};\hat{\pi_v})}{\tan(\hat{\pi_u})\tan(\hat{\pi_v})}\right[\tag{7.3}$$

what can be noted with equation 7.3 is that when there is an assumption of fixed effect model the $cov(\hat{\pi_u};\hat{\pi_v}) = 0$ for $u \neq v$ (Combescure et al., 2014). We must also note that this variance will hold if the pooled survival rate is normally distribution (that is if the pooled conditional probability is not close to one (Combescure et al., 2014)). The variance was used to get the 95% confidence interval

Appendix B

B.1 Estimation of the pooled median time

From Combescure et al. (2014) proposal it show how to estimate pooled median survival time, let us denote the median survival time by τ_m, using the linear interpolation of the summary survival curve between two survival time point $t_m and t_{m-1}$, where the pooled $S(\hat{t}_m < 0.5$ and $S(\hat{t_{m-1}} > 0.5$, then we can calculate the pooled median survival time as:

$$\tau_m = t_m - (t_m - t_{m-1}) \frac{S(\hat{t}_m) - 0.5}{S(\hat{t}_m) - S(\hat{t_{m-1}})} \tag{7.4}$$

R codes

C.1 R code

C.1.1 Univariate analysis

univariate analysis Data¡-read.csv(”C:
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smylo254.csv”) fixed effect model univariate that separate the effect sizes between time points
m6= rma(yi, vi, data=Data[Data$Time == 6,], method = "FE")$m12 = rma(yi, vi, data = Data[Data$Time==12,], method = ”FE”) m24= rma(yi, vi, data=Data[Data$Time == 24,], method = "FE")$m36 = rma(yi, vi, data = Data[Data$Time==36,], method = ”FE”) m60= rma(yi, vi, data=Data[Data$Time == 60,], method = "FE")$m120 = rma(yi, vi, data = Data[Data$Time==120,], method = ”FE”) summary(m6); summary(m12);summary(m24);summary(m36);summary(m60); summary(m120)
random effect model univariate that separate the effects sizes between time points
n6= rma(yi, vi, data=Data[Data$Time == 6,], method = "DL")$n12 = rma(yi, vi, data = Data[Data$Time==12,], method = ”DL”) n24= rma(yi, vi, data=Data[Data$Time == 24,], method = "DL")$n36 = rma(yi, vi, data = Data[Data$Time==36,], method = ”DL”) n60= rma(yi, vi, data=Data[Data$Time == 60,], method = "DL")$n120 = rma(yi, vi, data = Data[Data$Time==120,], method = ”DL”) the summary for survival proportion in fixed effect summary(n6); summary(n12);summary(n24);summary(n36);summary(n6
summary(n120)
forest plot of the fixed effect of eachh and every time point forest(m6, main=”month 6”) forest(m12, main=”month 12”) par(mfrow=c(1,2)) forest(m24, main=”month 24”) forest(m36, main=”month 36”) par(mfrow=c(1,2)) forest(m60, main=”month 60”) forest(m120, main=”month 120”)

forest plot of the random effect of eachh and every time point par(mfrow=c(1,2)) forest(n6, main="month 6") forest(n12, main="month 12") par(mfrow=c(1,2)) forest(n24, main="month 24") forest(n36, main="month 36") par(mfrow=c(1,2)) forest(n60, main="month 60") forest(n120, main="month 120")

C.1.2 Multivariate analysis

multivariate analysis Data5¡-read.csv("C:
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smylo2351.csv") Times ¡- Data5$TimeSurvival < -Data5$Survival Study ¡- Data5$studyPlottingthepublish
"n", ylim = c(0,1), xlab = "Time", ylab = "Survival")for(iinunique(sort(Study)))lines(Times[Study =
covariancedata(Data5)attach(Data5)results < -msurv(study, Time, NbRisk, Survival, confidence =
"Greenwood")resultsSummarysurvivalplotandconfidenceinterval1stforRandomeffect
to estimate summary survival analysis RandomEffectSummary¡- results$summary.randomRandomEffe
-results$summary.fixed FixedEffectSummary
Plotting the estimated summary survival curve with 95plot(Time, Survival, type="n",
col="grey", ylim=c(0,1),xlab="Time", ylab="Survival") for (i in unique(sort(Study)))
lines(Time[Study==i], Survival[Study==i], type="l", col="grey") points(max(Time[Study==i]),
Survival[Study==i Time==max(Time[Study==i])], pch=15) lines(RandomEffectSummary[,1],
RandomEffectSummary[,2], type="l", col="red", lwd=3) points(RandomEffectSummary[,1],
RandomEffectSummary[,3], type="l", col="red", lty=3, lwd=3) points(RandomEffectSummary[,1],
RandomEffectSummary[,4], type="l", col="red", lty=3, lwd=3)
Summary survival plot and confidence interval 1st for fixed effect FixedEffectSummary¡-
results$summary.fixedFixedEffectSummaryplot(Time, Survival, type = "n", col =
"grey", ylim = c(0,1), xlab = "Time", ylab = "Survival")for(iinunique(sort(Study)))lines(Time[Study
"l", col = "red", lwd = 3)points(FixedEffectSummary[, 1], FixedEffectSummary[, 3], type =
"l", col = "red", lty = 3, lwd = 3)points(FixedEffectSummary[, 1], FixedEffectSummary[, 4], type =
"l", col = "red", lty = 3, lwd = 3)