UNIVERSITI PUTRA MALAYSIA

PARAMETRIC AND NONPARAMETRIC INFERENCE FOR PARTLY INTERVAL-CENSORED FAILURE TIME DATA

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By

AZZAH MOHAMMAD ALHARPY

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Doctor of Philosophy

September 2013

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DEDICATIONS

To

My late father

Who has supported me all the way, May Allah rest his soul in heaven

My lovely mother

For her unlimited love, care and support

My brothers and sisters

For their great encouragement and support

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Doctor of Philosophy

PARAMETRIC AND NONPARAMETRIC INFERENCE FOR PARTLY INTERVAL-CENSORED FAILURE TIME DATA

By

AZZAH MOHAMMAD ALHARPY

September 2013

Chair: Noor Akma Ibrahim, PhD

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Survival analysis is used in many fields for analysis of data, particularly in medical and biological science. In this context the event of interest is often death, the onset of disease or the disappearance of disease's symptoms. The time to event is called failure time, and this failure time may be observed exactly and recorded or may occurred between two inspection times. Data that include both exact failure data and interval-censored data is called partly interval-censored data. This phenomenon often happens in clinical trials and health studies that are followed by periodic follow-ups. Comparison of survival functions is one of the main objectives in survival studies. Thus, this thesis focuses on the aspect of inferential comparison problem for survival functions in the existence of partly interval-censored failure time data. The research is divided into two parts, parametric and nonparametric inferences.

The parametric maximum likelihood estimator, and a score test and likelihood

ratio test for this kind of failure time data are constructed under Weibull distributions by using direct approach (without imputation) and indirect approach (with multiple imputation technique).

The nonparametric maximum likelihood estimator and the development of nonparametric test approach for comparison of survival function of two samples or more in the existence of partly interval-censored failure time data are constructed where the Turnbull self-consistency equation is modified and then subsequently used in the multiple imputation technique.

The behavior of parametric and nonparametric maximum likelihood estimators, and the development of parametric and nonparametric tests approach for comparison of survival function of two samples in the existence of this type of censored data are also studied under the non-proportional hazard by using Piecewise exponential distribution.

Simulation studies are carried out to assess the performance of the method and approach that have been developed. The simulation results indicate that the developed tests statistics work well and the good points of a certain method depend on a specific situation. A modified secondary data set from breast cancer study has been used to illustrate the proposed tests.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

PENTAKBIRAN BERPARAMETER DAN TAK BERPARAMETER BAGI DATA MASA KEGAGALAN TERTAPIS-SELANG SEBAHAGIAN

Oleh

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Analisis mandirian digunakan dalam pelbagai bidang untuk menganalisis data terutamanya dalam bidang sains perubatan dan biologi. Dalam konteks ini peristiwa yang sering menjadi tumpuan adalah kematian, permulaan penyakit atau kehilangan gejala penyakit. Masa sehingga peristiwa ini berlaku dikenali sebagai masa kegagalan dan masa kegagalan ini boleh dicerap dengan tepat dan direkodkan atau mungkin boleh berlaku diantara dua pemeriksaan. Data yang merangkumi kedua-dua jenis data kegagalan yang tepat dan juga tertapis selang dipanggil data tertapis-selang sebahagian. Fenomena ini sering berlaku dalam ujian klinikal dan kajian kesihatan yang disusuli dengan susulan berkala. Perbandingan diantara fungsi mandirian merupakan objektif utama dalam kajian mandirian. Yang demikian tumpuan tesis ini adalah untuk melihat dari aspek pentakbiran terhadap masalah perbandingan fungsi mandirian dengan kehadiran data masa kegagalan tertapis-selang sebahagian. Penyelidikan ini terbahagi kepada dua bahagian iaitu pentakbiran berparameter dan tak berparameter.

Penganggar kebolehjadian maksimum berparameter, ujian skor dan ujian nisbah kebolehjadian bagi data masa kegagalan jenis ini dibina berdasarkan taburan Weibull dengan menggunakan pendekatan secara langsung (tanpa imputasi) dan pendekatan secara tak langsung (teknik imputasi berganda).

Penganggar kebolehjadian maksimum tak berparameter dan pengembangan pendekatan ujian tak berparameter untuk perbandingan fungsi mandirian dua sampel atau lebih dengan kehadiran data masa kegagalan tertapis-selang sebahagian dibina dengan mengubahsuai persamaan kosistenan-kendiri Turnbull, seterusnya digunakan dalam teknik imputasi berganda.

Tingkah laku penganggar kebolehjadian maksimum berparameter dan tak berparameter dan perkembangan pendekatan ujian berparameter dan tak berparameter bagi membandingkan fungsi mandirian dua sampel dengan kehadiran data tertapis jenis ini dikaji juga dibawah model bahaya tak berkadaran menggunakan taburan eksponen cebis demi cebis.

Kajian simulasi telah dijalankan untuk menilai keupayaan kaedah dan pendekatan yang telah dibangunkan. Keputusan simulasi menunjukkan yang ujian statistik yang dibangunkan berfungsi dengan baik dan kelebihan sesuatu kaedah bergantung kepada situasi yang tertentu. Satu set data sekunder kanser payudara diubahsuai dan digunakan untuk mengilustrasi ujian yang telah dibangunkan.

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I certify that a Thesis Examination Committee has met on 20 September 2013 to conduct the final examination of Azzah Mohammad Alharpy on her thesis entitled "Parametric and Nonparametric Inference for Partly Interval-Censored Failure Time Data" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Doctor of Philosophy.

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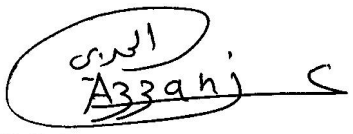
DECLARATION

I declare that the thesis is my original work except for quotations and citations which have been duly acknowledged. I also declare that it has not been previously, and is not concurrently, submitted for any other degree at Universiti Putra Malaysia or at any other institution.



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LIST OF ABBREVIATIONS

LRT	Likelihood Ratio Test
LRTD	Likelihood Ratio Test with Direct Approach
LRTI	Likelihood Ratio Test with Indirect Approach
MSE	Mean Square Erore
NPE	Nonparametric Estimate
NPMLE	Nonparametric Maximum Likelihood Estimator
PE	Parametric Estimate
PMLE	Parametric Maximum Likelihood Estimator
RE	Relative Efficiency
ST	Score Test
STD	Score Test with Direct Approach)
STI	Score Test with Indirect Approach)
W.I	With Imputation
W.O	Without Imputation

CHAPTER 1

INTRODUCTION

Survival analysis is a statistical method important in the analysis of life time, particularly in medical and biological sciences. The outcome variable of interest is time recorded for an event's occurence. In the context of medical and biological studies, the event of interest is often death, the onset of a disease or the disappearance of a disease's symptoms. The time to event of interest is called either survival time or failure time and the probability that the subject survives beyond a specified time is calculated by a basic formula called "survival function".

One of the complications which arises in survival analysis is the presence of censored data. Censoring occurs when the information about the failure time of some subjects is incomplete. Different circumstances can produce many types of censored data, including right-censored, left-censored and interval-censored data. Interval-censored data arises when the event of interest can not be immediately observed and it is only known to have appeared through a random interval of time.

Survival analysis with interval-censored data has been developed over the past three decades and written research is extensive. For example, Peto and Peto (1972) discussed partly interval-censored data whereby they treated their exact data as an interval-censored data, separating exact observation times by very short intervals. In an article by Peto (1973), the procedure was only to estimate the distribution function when data are interval-censored.

Turnbull (1976) described a scheme of censored failure time data and derived the self-consistency equation for computing the maximum likelihood estimator of survival function. Huang and Wellner (1995) proved the asymptotic normality of a

class of linear functions of the nonparametric maximum likelihood estimator of a distribution function with case I interval-censored data.

Interval-censored data are divided into many subcategories, including case I interval-censored data, case II interval-censored data, doubly interval-censored, mixed interval-censored and partly interval-censored. Partly interval-censored data is an important subcategory of interval-censored data. It arises in medical and health studies, which entail periodic follow-ups. Partly interval-censored data originates from an event of interest that is observed directly for some subjects, but for remaining subjects, the exact time of the event is unknown, except that it falls within a specific time interval.

1.1 Basic Formulation in Survival Analysis

The basic quantity employed to describe failure time phenomena is the survival function, the probability of an individual's survival beyond time t. It is defined as

$$S(t) = P(T > t) \tag{1.1}$$

where T is a non-negative random variable denoting the failure time.
If T is a continuous random variable, the survival function is the complement of a cumulative distribution function, that is,

$$S(t) = 1 - F(t) \tag{1.2}$$

where $F(t) = P(T \leq t)$. Furthermore, the survival function is the integral of the probability density function, that is,

$$S(t) = P(T > t) = \int_t^{\infty} f(u)du \tag{1.3}$$

thus

$$f(t) = -\frac{d\,S(t)}{dt} \quad . \tag{1.4}$$

When T is a discrete random variable a different technique is required. Discrete random variables in survival analysis created due to rounding off measurements, collection of failure times into intervals, or when lifetime refers to an integral number of units. Let T be the discrete random variable taking values, where $0 = t_0 < t_1 < t_2 < \cdots$, with probability mass function $p(t_j) = P(T = t_j)$ $j = 1, 2, \cdots,$. Therefore, the survival function of T is

$$S(t) = P(T > t) = \sum_{t_j > t} p(t_j) \quad . \tag{1.5}$$

Additionally, the hazard function and the cumulative hazard function of T are also fundamental in survival analysis. Hazard function is also known as the conditional failure rate in reliability and can be defined by

$$h(t) = \lim_{\Delta t \to 0} \frac{1}{\Delta t} P(t \leq T < t + \Delta t | \, T \geq t) \quad . \tag{1.6}$$

If T is a continuous random variable, then

$$h(t) = \frac{f(t)}{S(t)} = -\frac{d \ln[S(t)]}{dt} \quad . \tag{1.7}$$

A related function is the cumulative hazard function $H(t)$, defined by

$$H(t) = \int_o^t h(u)\, du = -\ln[S(t)] \quad . \tag{1.8}$$

It is easy to see that

$$S(t) = \exp[-H(t)] = \exp[-\int_0^t h(u)\, du] \quad . \tag{1.9}$$

When T is a discrete random variable, the hazard function is given by

$$h(t_j) = P(T = t_j | \, T \geq t_j) = \frac{p(t_j)}{S(t_{j-1})} \quad j = 1, 2, \ldots . \tag{1.10}$$

And the cumulative hazard function $H(t)$ is defined as

$$H(t) = \sum_{t_j \leq t} h(t_j) \quad . \tag{1.11}$$

Note that, $S(t)$, $h(t)$ or $H(t)$ uniquely determines the distribution of T.

1.2 Types of Interval-Censored Data

Interval-censored data is one of the obstacles which arises in survival analysis. There are several different types of interval-censored data. They are as follows:

1. Case I interval-censored data, also called current status data, arises when each individual is subjected to observation only at a single follow-up time, and thus, the event of interest (failure) is only observed either to have or have not occurred before the observation time. That is, the failure time of interest is either left- or right-censored data respectively (Keiding, 1991; Groeneboom and Wellner, 1992; Koul and Yi, 2006).

   Case I interval-censored data usually occur in tumorigenicity tests. In these tests, the tumor start time of animals is commonly of prime interest but not observable. Instead, tumor status is commonly known at death (either natural death or euthanization for scientific study). Thus, the tumor start time is expected only to be less or greater than the death time. There are many authors who discussed the current status data arising from survival studies such as Huang and Wellner (1995); Huang (1996), Rossini and Tsi-

atis (1996), Lin et al. (1998), Shen (2000), Ghosh (2001), Martinussen and Scheike (2002), Xue et al. (2004) and Sun (2006).

2. Case II interval-censored data, also called general interval-censored data, is defined as data which refers to a situation when the event of interest cannot be immediately observed and is only known to have appeared through a random interval of time. Left (right) censoring is a special case of interval censoring in which the left (right) end point is $0(\infty)$.

   Case II interval-censored data arises in several of medical and health studies. For example, in a study which compares time to cosmetic deterioration of breasts for breast cancer patients treated with radiotherapy and radiotherapy plus chemotherapy, patients were examined at each clinical visit for breast retraction. The breast retraction is only known to take place between two clinical visits or right censored at the end of the study. The objective of the study is to compare the patients who received adjuvant chemotherapy to those who did not and to decide whether chemotherapy affects the rate of deterioration of the cosmetic state (Finkelstein, 1986; Pan, 2000; Lim and Sun, 2003; Huang et al., 2008).

3. Doubly interval-censored data refers to the survival time of interest, which is the elapsed time between two related events called the initial and the end events, and the observations on the occurrences of both events could be interval-censoring (Gruttola and Lagakos, 1989; Sun, 1997, 2001, 2004).
   If X is the time to the initial event in which $X \in (L_X, R_X]$ and Y is the time to the end event in which $Y \in (L_Y, R_Y]$, then the random variable $T = Y - X$ corresponds to the survival time of interest. Doubly interval-censored data is reduced to right-censored or interval-censored data if the occurence of the initial event was observed exactly (Deng et al., 2009). This kind of data

often arise in many fields such as biometry studies and reliability research. The articles that addressed the doubly interval-censored data arising from survival studies include Kim et al. (1993), Gomez and Lagakos (1994), Li and Yu (1997), Gomez and Call (1999), Fang and Sun (2001), Sun et al. (2004), Sun (2006) and Zhang et al. (2009).

4. Mixed interval-censored data refers to the survival time of interest, which is observed either to belong to an interval, or to be in right-censoring (Zhao and Sun, 2004).

5. Partly interval-censored data arise when the exact failure times are observed of some subjects, but for the remaining subjects, the failure time of interest is not observable, but is only known to be bracketed between two examination times (Huang, 1999). An example of this type of partly interval-censored data is presented by the Framingham Heart Disease study. In this study, times of the first occurrence of the subcategory angina pectoris in coronary heart disease patients are of interest. For some patients, the event time is recorded precisely, but for the remaining patients, time is recorded only between two clinical examinations (see Feinleib et al., 1975; Odell et al., 1992). More details about this kind of data is presented in Chapter 3.

1.3 Independent Interval Censoring

Independent interval censoring is a factual assumption in survival analysis. Independent interval censoring is the condition whereby the method that generates the censoring is independent of the subject's failure time distribution. For instance, T is failure time of interest and L and R are the two observed values such that $T \in (L, R]$. Then the independent censoring process for interval-censored data can

be expressed by

$$P(L < T \leq R | L = l, R = r) = P(l < T \leq r) \quad .$$

. This means the joint survival function of the two observed values L and R is free from any parameters contributory in the survival function of T. More importantly, it should be noted that the independent interval censoring is non-informative interval censoring while the opposite is not always true (Betensky, 2000; Oller et al., 2004; Sun, 2006).

1.4 Proportional and Non-proportional Hazards Model

Proportional hazards model is a common semi-parametric regression model used for analyzing survival data, proposed by Cox (1972) to examine the effect of predictor variable on survival time. Proportional hazards model has extensively been used in medical testing analysis and reliability engineering.

Proportional hazards model is usually written in terms of the hazard model, (see Kleinbaum, 1996).

$$h(t, \mathbf{X}) = h_0(t)\, e^{\sum_{i=1}^{p} \beta_i X_i} \tag{1.12}$$

where $h_0(t)$ is called baseline hazard and $e^{\sum_{i=1}^{p} \beta_i X_i}$ is called the exponential. If the baseline hazard is specified, the model is called parametric model, but if the baseline hazard is unspecified, the model is called nonparametric model.

The proportional hazards model (Cox and Oakes, 1984) is expressed by

$$h_1(t, \mathbf{X}) = \psi(\mathbf{X})\, h_0(t) \tag{1.13}$$

in which the explanatory vector $\mathbf{X}$ is constant over time for any subject and $h_0(t)$ is the hazard for the subject under the standard conditions, $\mathbf{X} = \mathbf{0}$ and we require $\psi(\mathbf{0}) = 1$. Then, the survival function under the proportional hazards model is given by

$$S_1(t, \mathbf{X}) = [S_0(t)]^{\psi(\mathbf{X})} \quad . \tag{1.14}$$

Here $S_0(t)$ is a survival function corresponding to the hazard function $h_0(t)$. If $\psi(\mathbf{X}) = 1$, there is no difference between the two survival curves, and if $\psi(\mathbf{X}) > 1$, then the subject with survival function 1 has a lower survival rate. Correspondingly, if $\psi(\mathbf{X}) < 1$, then the subject with survival function 1 has a higher survival rate.

Comparatively, in Cox's non-proportional hazards model, the hazard ratio is represented as a step function of time. The hazard is given by

$$h(t, x) = h_0(t)\, exp\,(\sum_{i=1}^{p}(\beta_i + \gamma_{ji})x_i) \tag{1.15}$$

where $j = (1, \cdots, r)$, $\gamma_{1i} = 0$. In non-proportional hazards model, the hazard ratio will be constant within each of the r pre-specified time intervals but change between the intervals. That means, the hazard ratio equals to $exp\,(\beta_i)$ in the first interval and $exp(\beta_i + \gamma_{ji})$ in the subsequent intervals for $j = 2, \cdots, r$ (Basar, 2006).

In this thesis we assume the parametric model is without covariate. This means the failure time satisfies a specific distribution . In the case of proportional hazards model we presume that the failure times follow Weibull distribution and the hazard ratio between two distributions is

$$\frac{h_2(t)}{h_1(t)} = exp(\beta), \quad \text{for all} \;\; t \geq 0.$$

This kind of model is applied in Chapter 3.

In the case of non-proportional hazards model we suppose that the failure times follow a piecewise exponential distribution and the hazard ratio between two distributions with two intervals is

$$\frac{h_2(t)}{h_1(t)} = exp\,(\beta_1)\; I_{(t \leq t_0)} + exp\,(\beta_2)\; I_{(t > t_0)}.$$

Where t_0 represents the cut point. If $\beta_1 = 0$ and $\beta_2 \neq 0$, then we have late hazard difference, and if $\beta_1 \neq 0$ and $\beta_2 = 0$, then we have early hazard difference. If $\beta_2 = -\beta_1$, then we have cross hazard. This kind of model is applied in Chapter 5.

1.5 Weibull Distribution

The Weibull distribution is a commonly used distribution for studying lifetime models, biological and medical sciences and reliability. Let T be a random variable following the Weibull distribution with shape parameter a and scale parameter b. The Weibull distribution density function (Raymond, 1977) is given by

$$f(t) = \frac{a}{b}(\frac{t}{b})^{a-1}\, exp\,[-(\frac{t}{b})^a] \quad t > 0, a > 0, b > 0 \tag{1.16}$$

Figure 1.1 shows the density functions for different Weibull distribution. The cumulative Weibull distribution function and survival function are given by

$$F(t) = 1 - exp\,[-(\frac{t}{b})^a] \quad t > 0, a > 0, b > 0 \tag{1.17}$$

and

$$S(t) = exp\,[-(\frac{t}{b})^a] \quad t > 0, a > 0, b > 0 \tag{1.18}$$

respectively.

The hazard function of Weibull distribution is given by

$$h(t) = \frac{a}{b}\,(\frac{t}{b})^{a-1} \quad t > 0, a > 0, b > 0 \tag{1.19}$$

Figure 1.2 shows the hazard functions for different Weibull distribution. It is easy to see that the Weibull distribution reduces to the exponential distribution and has constant hazard over time if the shape parameter $a = 1$. The hazard function increases over time if $a > 1$. The hazard function decreases over time if $a < 1$.

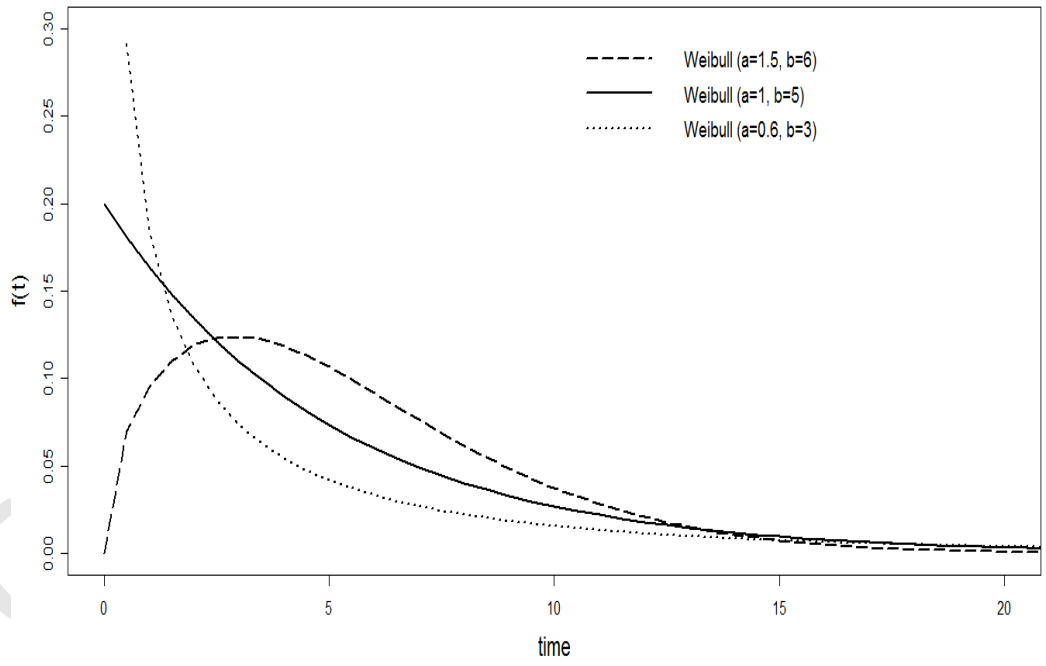

Figure 1.1: Density Functions for Different Weibull Distribution.

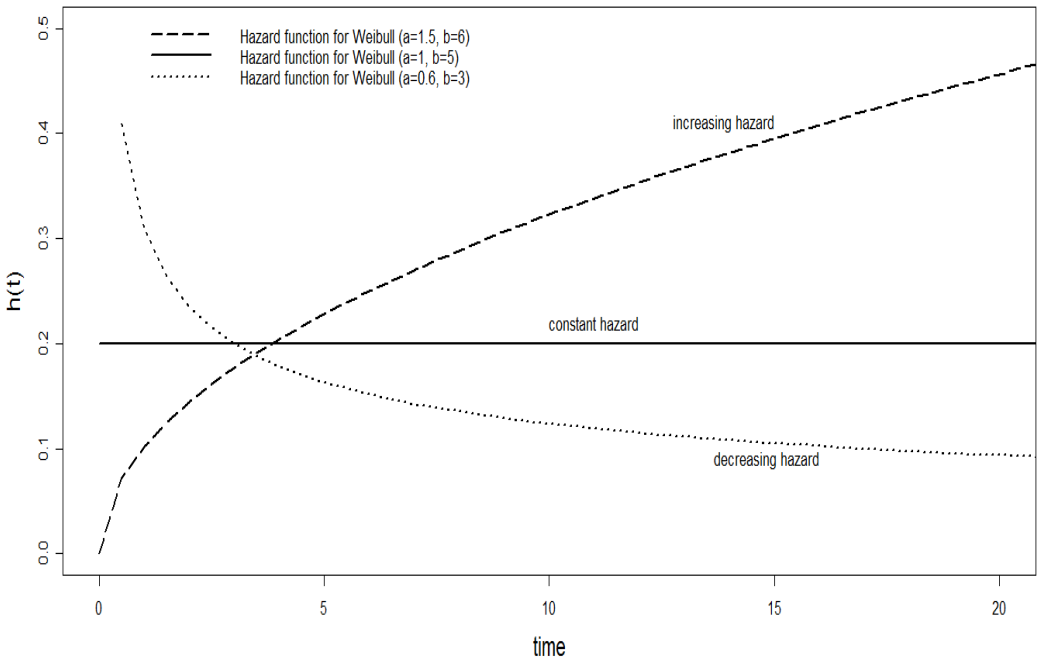

Figure 1.2: Hazard Functions for Different Weibull Distribution.

1.6 Multiple Imputation

Imputation method is one of common tools to solve missing values. Missing values arise in many fields of study. For example, in medical and health studies, it is required for the participants to undergo periodic follow-ups for the examination of characteristic related to condition of interest. The missing values permanently occur for several reasons. For handling the missing values there are various imputation methods such as single imputation, multiple imputation and others.

Single imputation is often applied because it is intuitively attractive. In single imputation, we fill in each missing value by predicted value. The obvious shortcoming in single imputation is that we replace the missing values by a single values and then treat it as if it were a true values. As a result, single imputation ignores uncertainty and always underestimates the variance. Multiple imputation rectifies

this shortcoming, by taking into account both within imputation uncertainty and between imputation uncertainty. In this thesis the focus will be on multiple imputation.

Multiple imputation technique was developed by Rubin (1987) as a general technique for handling data sets with missing values. Application of the technique requires three steps: imputation, analysis and pooling.

Imputation step: Impute (fill in) the missing value several times, creating many augmented data sets.

Analysis step: Analyze each augmented data set separately.

Pooling step: Integrate the analysis results into a final result.

More formally, suppose that we are interested in estimating an unknown parameter vector θ. Let $\hat{\theta}$ be an estimator of θ when the data set is complete and $\hat{\Sigma}$ is a covariance estimator associated with $\hat{\theta}$. Now, we use multiple imputation to obtain multiple sets (Y sets) of complete data from the given incomplete data set. Then, we will obtain Y estimates, $\left(\hat{\theta}_y, \hat{\Sigma}_y\right)$, $y = 1, \cdots, Y$.

Rubin's multiple imputation estimators are given by

$$\hat{\theta}_* = \sum_{y=1}^{Y} \frac{\hat{\theta}_y}{Y} \quad ,$$

where $\hat{\theta}_*$ is the estimate of θ based on the Y imputation, and

$$\hat{\Sigma}_* = \frac{1}{Y}\sum_{y=1}^{Y} \hat{\Sigma}_y + \left(1 + \frac{1}{Y}\right) \sum_{y=1}^{Y} \frac{\left(\hat{\theta}_y - \hat{\theta}_*\right)\left(\hat{\theta}_y - \hat{\theta}_*\right)^T}{Y - 1}$$

is the estimate of the covariance, where the first term is the average within the

imputation covariance associated with the estimate, and the second term is the between imputation covariance of the estimate multiplying by $\left(1+\frac{1}{Y}\right)$, where the factor $\left(1+\frac{1}{Y}\right)$ is an adjustment for using a finite number of imputations.

The multiple imputation method has been discussed in research analyzing interval-censored failure time data. This method is used to reduce the interval-censored data to right-censored data, which can be handled by using specified methods for right-censored data (for an example see Pan, 2000; Chen and Sun, 2010). This method is also used to reduce the interval-censored data to exact data, which can be handled by using specified methods for exact data (for an example see Huang et al., 2008). There are many authors who employed the imputation methods for interval-censored data such as Dorey et al. (1993), Satten et al. (1998), Betensky and Finkelstein (1999), Bebchuk and Betensky (2000) and Pan (2001).

1.7 Problem Statement

Many statistical approaches have been developed to solve the problems that arise in the survival analysis. One of these problems is comparison of survival distribution for two samples or more when data are incomplete. In most previously published research the comparison problem of survival distribution for two samples or more has been solved for cases with right-censored data and interval-censored data. Multiple imputation technique is one method that has been used to solve the comparison problem when the data are right-censored or interval-censored. In contrast, not many research has been considered for partly interval-censored data and it is still ongoing but so far limited. For example, Kim (2003) used the proportional hazard model for regression analysis of partly interval-censored data. Elfaki et al. (2012) studied the parametric Cox's proportional hazard model for partly interval-censored data. Both the articles discuss a parametric comparison

of survival function by fitting proportional hazard model regression. Zhao et al. (2008) discussed nonparametric test for partly interval-censored data and evaluated their proposed test under proportional hazard model using simulation studies.

It should be noted that the previous published researches were focused on parametric and nonparametric tests for proportional hazard model only and to our knowledge, there is no any application of multiple imputation to partly interval-censored data so far. This thesis is motivated by the idea that existing comparison problem for survival distribution of two samples or more in the presence of partly interval-censored data is needed to examine the impact of imputation on the results.

In this thesis, the focus will be on the problem of comparing survival distributions of two samples or more in the presence of partly interval-censored failure time data by using the multiple imputation technique under proportional and non-proportional hazards model. This research will be divided into two parts, the first part will be devoted to the parametric test for partly interval-censored data via multiple imputation. We will construct a parametric maximum likelihood estimator using Weibull distribution with partly interval-censored data in order to carry out the test under the proportional hazards model. Also, we will construct a parametric maximum likelihood estimator for piecewise exponential distribution with partly interval-censored data in order to implement the test under the non-proportional hazards model.

The second part of the research will be devoted to the nonparametric test for partly interval-censored data via multiple imputation. We will modify the self-consistency algorithm in terms of partly interval-censored data and we will construct the non-

parametric test in the presence of partly interval-censored data and analyze the generalized log-rank test via multiple imputation. We will then study the proposed test under proportional and non-proportional hazards model.

1.8 Objectives

The aim of this research is to establish parametric and nonparametric tests for comparing survival functions of two samples or more in the presence of partly interval-censored data via multiple imputation technique.
The main objectives of this study are as follows:

1. To establish the parametric and the nonparametric estimators of survival function in the presence of partly interval-censored data.

2. To develop a parametric and a nonparametric tests in the presence of partly interval-censored data via multiple imputation technique to address the comparison problem for two samples or more under proportional hazards model using Weibull distribution.

3. To develop a parametric and a nonparametric tests in the presence of partly interval-censored data via multiple imputation technique to address the comparison problem for a two-sample under non-proportional hazards model using piecewise exponential distribution.

4. To conduct a simulation study to assess the properties of the survival function estimates and to investigate the performance of the proposed tests under the proportional hazards model and non-proportional hazards model.

5. Application of the developed models to a modified real data set.

1.9 Outline of Thesis

This thesis is organized into six chapters. Chapter 2 provides a review of current related literature such as the research conducted on parametric and nonparametric tests which compare two samples or more in the presence of interval-censored failure time data.

Chapter 3 starts with the description for partly interval-censored data. Then, the parametric maximum likelihood estimator (PMLE) for survival function is constructed under Weibull distribution. Following that, parametric tests such as the score test and the likelihood ratio test are performed in the presence of the partly interval-censored data using two approaches, direct (without imputation) and indirect (with imputation). Conclusions are then recorded based on the simulation data and a modified secondary data set from breast cancer.

Chapter 4 studies a nonparametric test with partly interval-censored data via multiple imputation. Turnbull's self-consistency algorithm is modified in terms of partly interval-censored data to construct the nonparametric maximum likelihood estimator (NPMLE) for survival function. Then, the generalized log-rank test is carried out in the presence of partly interval-censored data using multiple imputation technique. Following that, a comparison is made between a generalized log-rank test and Huang's test under partly interval-censored data. Finally based on the simulation data and a modified secondary data set from breast cancer the conclusions are drawn.

Chapter 5 concentrates on the parametric and nonparametric tests under the non-proportional hazards model with partly interval-censored failure time data via multiple imputation technique. The PMLE for survival function is constructed under

piecewise exponential distribution in the presence of the partly interval-censored data. Then, the parametric tests such as the score test and the likelihood ratio test are implemented in the presence of partly interval-censored data using multiple imputation technique. Following that, a generalized log-rank test with partly interval-censored data is applied under non-proportional hazards model. Additionally, the simulation data and a modified secondary data set from breast cancer are used. Conclusions from this chapter are drawn.

Finally, Chapter 6 summarizes the study and suggests some recommendations for further research.

It should be mentioned that all simulation studies were implemented by using the R programming language.

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