UNIVERSITI PUTRA MALAYSIA

PARAMETRIC CURE FRACTION MODELS FOR INTERVAL–CENSORING WITH A CHANGE–POINT BASED ON A COVARIATE THRESHOLD

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By

FAUZIA ALI TAWEAB

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

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DEDICATION

To

My late father

Who has supported me all the way, may ALLAH rest his soul in heaven

My lovely mother

For her love, care and support

My sisters and brothers

For their great encouragement

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

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FAUZIA ALI TAWEAB

March 2015

Chairman: Professor Noor Akma Ibrahim, PhD

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Survival models with a cure fraction have received considerable attention in recent years. It becomes a very useful tool for handling situations in which a proportion of subjects under study may never experience the event of interest. Cure fraction models for interval-censored data are less developed compared to the right-censoring case. Moreover, most of the existing cure fraction models share in common the assumption that the effect of a covariate is constant in time and over the range of the covariate. This assumption is not completely valid when a significant change occurs in subjects' failure rate or cure rate. Therefore, this study focuses on developing several classes of parametric survival cure models for interval-censored data incorporating a cure fraction and change-point effect in covariate.

The analysis starts with the extension of the existing cure models; mixture cure model (MCM) and Bounded cumulative hazard (BCH) model, with fixed covariates in the presence of interval-censored data. Then, this research introduces a modified cure model as an alternative to the MCM and BCH model. The proposed model has sound motivation in relapse of cancer and can be used in other disease models. The parametric maximum likelihood estimation method is employed to verify the performance of the MCM within the framework of the expectation-maximization (EM) algorithm while the estimation methods for other models are employed in a simpler and straightforward setting.

In addition, the models are further developed to accommodate the problem of change-point effect for the covariate and a smoothed likelihood to obtain relevant estimators is proposed. An estimation method is proposed for right-censored data, and the method is then extended to accommodate interval-censored data. Simulation studies are carried out under various conditions to assess the performances of the models that have been developed. The simulation results indicate that the proposed models and the estimation procedures can produce efficient and reasonable estimators. Application of suggested

models to a set of gastric cancer data is demonstrated. The proposed models and approaches can be directly applied to analyze survival data from other relevant fields.

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

MODEL PECAHAN SEMBUH BERPARAMETER BAGI TERTAPIS–SELANG DENGAN KESAN TITIK – UBAH DALAM KOVARIAT

Oleh

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Kebelakangan ini model mandirian dengan pecahan sembuh telah menerima banyak perhatian. Ianya telah menjadi alat yang penting untuk menangani keadaan yang mana sebahagian daripada subjek dalam kajian mungkin tidak mengalami peristiwa yang menjadi perhatian. Model pecahan sembuh bagi data tertapis – selang tidak banyak kemajuan jika dibandingkan dengan kes tertapis – kanan. Lagipun, kebanyakan model pecahan sembuh yang sedia ada mempunyai andaian yang kesan kovariat adalah malar mengikut masa dan merentangi kovariat. Andaian ini tidak sah apabila berlaku perubahan signifikan ke atas kadar sembuh atau kadar kegagalan bagi subjek. Justeru, tumpuan kajian ini adalah untuk membina beberapa kelas model sembuh mandirian berparameter bagi data tertapis – selang dengan mengambilkira pecahan sembuh dan kesan titik – ubah dalam kovariat.

Analisis bermula dengan melanjutkan model yang sedia ada; model campuran sembuh (MCS) dan model kumulatif bahaya terbatas (KBT) dengan kovariat tak berubah dengan mengambilkira kehadiran data tertapis-kiri,-selang dan-kanan. Kajian diteruskan dengan memperkenalkan model terubah saui sebagai alternatif kepada model MCS dan KBT. Model yang dicadangkan mempunyai motivasi yang baik bagi kambuh kanser dan boleh digunakan dalam model penyakit yang lain. Kaedah anggaran kebolehjadian maksimum berparameter digunakan untuk mengesahkan prestasi MCS dengan melaksanakan algoritma memaksimumkan – jangkaan (MJ) manakala kaedah anggaran bagi model yang lain dilakasanakan secara lebih mudah.

Disamping itu model ini dibangunkan selanjutnya untuk mengambilkira masalah kesan titik –ubah dalam kovariat dengan mencadangkan kebolehjadian licin untuk memperoleh anggaran. Satu kaedah anggaran diusulkan untuk data tertapis – kanan dan kaedah ini diperluaskan untuk menampung data tertapis – selang. Kajian simulasi dijalankan di bawah pelbagai keadaan untuk menilai prestasi model yang telah dibangunkan. Keputusan simulasi menunjukkan bahawa model dan prosedur anggaran yang dicadangkan dapat menghasilkan penganggar yang cekap dan wajar. Model telah

diterapkan dengan menggunakan data kanser gastrik. Model dan pendekatan yang dicadangkan boleh diterapkan terus untuk menganalisis data mandirian dari bidang lain yang relevan.

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This thesis submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfillment of requirement for the degree of Doctor of Philosophy. The members of the Supervisory committee were as follows:

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LIST OF ABBREVIATIONS

MCM	Mixture Cure Model
NMCM	Non-Mixture Cure Model
BCH	Bounded Cumulative Hazard model
GNMCM	Geometric Non-Mixture Cure Model
EM	Expectation Maximization algorithm
PMLE	Parametric Maximum Likelihood Estimation
MSE	Mean Square Error

CHAPTER I

INTRODUCTION

1.1 Background of Study

Survival analysis is one group of statistical techniques that is playing an increasingly important role in many fields of medical and equivalent areas of research. It is a collection of statistical techniques for data analysis, in which the response variable of interest, T, is the time taken until the event of interest occurs. The data can be about time till death, time passing until the patient responds to therapy, time passing till disease relapse, or time to disease development. Depending on the fields of application, survival analysis has other descriptions, such as event history, duration analysis, failure time, and reliability analysis. The most common feature of time-to-event data analysis is that some, or even all, $t_i, i = 1, 2, \dots, n$ are censored due to a variety of potential reasons, e.g., subject not experiencing the event before study ends, subject quitting follow up during the period of the study, or subject withdrawing from the study.

In medical studies, survival models are widely used to analyze time-to-event data in which subjects are followed over a certain time period and the time till the occurrence of an event of interest is recorded. For example, a study may analyze the time from surgery to recurrence of tumor in breast cancer patients or the time from treatment to infection in patients with renal insufficiency. It is typically assumed that every study subject will eventually experience the event of interest if she/he is observed long enough. However, in reality the event may not occur with some subjects even after a very long period of time. For instance, in prostate or breast cancer studies, it is common for a proportion of the patients never to experience the event of interest (recurrence) after treatment. In this case, the patients are not censored in the traditional sense and are hence confidently assumed to be cured. Therefore, traditional survival models like the accelerated failure time and the proportional hazard model of Cox are not appropriate for such cases and this type of data. Consequently, cure rate models have been basically developed for handling this type of data. In the cure model, censored group is divided into two sets: those that are event-free, thus cured and those that will evenatually have events if they could be followed for a long enough period of time.

Two major approaches to model survival data with cure rate. The first one is the mixture cure model (MCM), which was proposed by Boag (1949) on the basis of the assumption that the cohort of the study is composed of susceptible subjects and cured subjects. The second is the non-mixture cure model (NMCM) which was established by Yakovlev et al. (1993) and was, for long, referred to as the Bounded Cumulative Hazard (BCH) model. It was motivated by the underlying biological mechanism and developed based on the assumption that number of cells of cancer which remain active after cancer treatment follows Poisson distribution. These two models are related and the BCH model can be transformed into the standard mixture cure model when the cure fraction is specifically specified.

Both cure models have been extensively studied and applied in medical research. However, the so-far existing cure models do not take advantages of some additional

sources of data that may provide or elucidate further information about the cure rate such as the change-point phenomena. In reality, cured individuals may exist in change-point situations. For example, in assessing the possibility of a patient cured under a treatment depending on an individual's biomarker, one may suspect that for patients with the biomarker value above a certain threshold, the treatment works more or less effectively (Ma, 2011). As another example, rates of cancer incidence stay stable, relatively, in young individuals but drastically change later to a specific age threshold (MacNeill and Mao, 1995). So, a cure model that allows for a change-point effect, either in hazard rate or in covariates, should be considered for the analysis of these, and similar, phenomena.

1.2 Scope of Study

The focus of this thesis is on the problem of cure fraction estimation in the presence of censored data and change point effect in covariates. This research will be divided into two parts; the first part will be devoted to extend several parametric cure models to accommodate interval-censored data in the presence of time-independent covariates. A parametric maximum likelihood estimator is constructed using log-normal distribution. The second part of this study will be devoted to develop these models to allow for a change-point effect in a covariate. An estimation method will be proposed for right censored data and the method will be further extended to accommodate interval censored data.

1.3 Problem Statement

Due to advances in cancer treatment, many cancer patients get cured of their cancer. Therefore, one of the most important reasons for using cure models is that cure fraction is a very interesting measure for someone suffering from cancer that gives valuable information to her/him. Furthermore, by using cure models, information about the cure fraction besides the uncured subjects' survival function can be obtained and by looking into changes in both of these estimates a lot more can be understood about the change in survival rates than by looking only into the probability of survival.

Survival models accounting for patients who are expected to be cured are growing fast because these models handle the proportion of cured patients which is highly important for our conception of prognosis in possibly terminal diseases and which can reveal unknown health problems associated with the study population.

Many cure models have been developed to handle survival data with cure fraction. Parametric approach is one method that has been used to estimate the cure probability and survival function for uncured subjects. So far, in most previously published research parametric cure models have been proposed for right censored data. Moreover, the existing cure models assume that the covariates act smoothly on the cure rate or the survival/hazard function. In practice, this assumption is not always adequate in the whole range of a covariate and the covariate may be dichotomized according to a threshold that may be fixed or have to be estimated from data. An important generalization of the cure models is to allow the survival function or cure fraction to depend to the strata defined by the covariates whose effect vary over time. In

consequence, this research investigates how to incorporate a change-point effect in covariate into several classes of parametric cure models in presence of two types of censoring (right and interval) and hence develops new cure models. This study also proposes a parametric estimation procedure for these models.

1.4 Research Objectives

The aim of this research is to develop parametric cure models to accommodate the problem of change-point effect in covariates for survival time with right-, and interval-censored data. The parametric approach to the analysis will be based on the log-normal distribution. Therefore, the main objectives of this study are:

- To extend the parametric cure models; Mixture Cure Model (MCM) and Bounded Cumulaive Hazrad (BCH) model to accommodate interval-censored data in the presence of fixed covariates.
- To extend and modify the non-mixture cure model (NMCM) as an alternative to the MCM and BCH model. A parametric method of the model is proposed for
    - Right-censored data.
    - Interval-censored data.
- To extend and develop the MCM and BCH model that incorporates a change-point effect in covariate in the presence of
    - Right-censored data.
    - Interval-censored data.
- To extend and develop the modified model (GNMCM) that allows for a change-point effect in covariate in the presence of
    - Right-censored data
    - Interval-censored data.
- To propose parameter estimation procedures for the developed models.
- To evaluate the performances of the developed cure models through simulation study.

1.5 Outline of the Thesis

This thesis is divided into two main sections, each handling several important approaches to cure rate estimation, applied to censored data. The first section handles parametric estimation of the cure fraction for interval-censored data based on MCM and BCH in presence of fixed covariates. This part also introduces a modified class of cure models. The second part addresses extension of those classes of cure models to accommodate a change-point effect in a covariate. Estimation methods are proposed for right-censored, and the methods are naturally extended to accommodate interval-censored data.

In Chapter 2, a review of the literature related to the main theme of this research is presented. Sections 2.1 and 2.2 address the survival data and common censoring types with particular attention to interval and right censoring, respectively. An overview of a number of broadly-used survival cure models is presented in Section 2.3. Section 2.4

describes the problem of change-point. In Section 2.5, the estimation method, Expectation Maximization (EM) algorithm is introduced.

Chapter 3 presents a general view of the parametric approach to cure rate estimation with censored data. The log-normal distribution is used to express the uncured individuals' distributional function. This research uses the maximum likelihood for estimation of the parameters of interest. We then conduct a simulation study for each scenario in this part of the research to evaluate the estimation method's performance and then compare the performances of the different models. Sections 3.2 elaborate on the derivation of the MCM for interval-censored data. Section 3.2.1 discusses the maximum likelihood parametric estimation method in the MCM. In Section 3.3 an elaboration is given on the parametric BCH model for right-censored data. Similar procedure is presented in Section 3.3.2 for interval-censored data. Section 3.4 introduces a modified class of cure rates models which can be considered as an alternative to the MCM and BCH model. lastly, a brief description of the parametric method is introduced in Section 3.6.

Parametric estimation of the mixture cure model with a change point effect in covariates based on censored-data is presented in Chapter 4. In Section 4.2 an elaboration is given on the parametric approach to cure fraction estimation for right censoring and log-normal distribution. Section 4.3 discusses the same procedure illustrated in Section 4.1 but with interval-censored data. The major study findings and conclusions are provided in Section 4.4.

Chapter 5 discusses parametric estimation of the two classes of cure models with a change-point effect in covariate. Section 5.2 gives a description of the parametric estimation technique for the BCH model under right censoring, and interval censoring (Section 5.2.2). Then, Section 5.3 discusses the parametric estimation approach for the second class of cure models (GNMCM). The main findings and conclusions of the research work are given in Chapter 6 together with some recommendations for future studies.

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