ANALYZING SURVIVAL DATA FOR SEQUENTIALLY RANDOMIZED DESIGNS

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Sequentially randomized designs are becoming common in biomedical research, particularly in clinical trials. These trials are usually designed to evaluate and compare the effect of different treatment regimes. In such designs, eligible patients are first randomly assigned to receive one of the initial treatments. Patients meeting some criteria (e.g. no progressive diseases) are then randomized to receive one of the maintenance treatments. Usually, the procedure continues until all treatment options are exhausted. Such multistage treatment assignment results in dynamic treatment regimes consisting of initial treatment, intermediate response and second stage treatment. However, methods for efficient analysis of sequentially randomized trials have only been developed very recently. As a result, earlier clinical trials reported results based only on the comparison of stage-specific treatments.

We first propose to use accelerated failure time and proportional hazards models for estimating the effects of treatment regimes from sequentially randomized designs. Based on the proposed models, differences between treatment regimes in terms of their hazards are tested. We investigate the properties of these methods and tests in a Monte Carlo simulation study. Finally the proposed models are applied to the long-term outcome of the high risk neuroblastoma study.

We then extend the proportional hazards model to a generalized Cox proportional hazards model that applies to comparisons of any combination of any number of treatment regimes regardless of the number of stages of treatment. Contrasts of dynamic treatment regimes are tested using the Wald chi-square method. Both the model and Wald chi-square

tests of contrasts are illustrated through a simulation study and an application to a high risk neuroblastoma study to complement the earlier results reported on this study.

Chronic diseases such as cancer and cardiovascular diseases are major causes of mortality and morbidity in the United States and in the world. Sequentially randomized designs are commonly used in clinical studies investigating treatments of chronic diseases such as cancer, AIDS, and depression. The public health significance of the methodologies proposed in this research is to allow efficient analysis of data from such studies and thereby enhance the discovery of efficient maintenance and eradication strategies for chronic diseases.

Keywords: Accelerated failure time model, Cox proportional hazards model, Dynamic treatment regime, High risk neuroblastoma study, Proportional hazards model, Sequentially randomized design, Time-dependent covariates.

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PREFACE

This dissertation is about the estimation of the survival quantities (e.g. hazards, survival probabilities) under various regimes and effective contrasts of different regimes in sequentially randomized clinical trials. I have been very fortunate to be surrounded by people, who helped me a lot throughout my dissertation research.

First of all, I would like to express my sincere gratitude to my advisor, Dr. Abdus S. Wahed, who contributed his ideas and comments on various theoretical and textual issues to the quality of this dissertation. It was also him, who first exposed me to the statistical topic about sequentially randomized designs. With my interest in this topic blooming, we achieved the accomplishment showed in this dissertation. Because of his confidence in me, I blundered through the tough part of my research.

I was also much beholden to my dissertation committee members, Dr. Howard E. Rockette, Dr. Joseph P. Costantino, and Dr. Joyce Ho Chang, for their insightful opinions and timely feedbacks.

Heartily gratefulness should also be given to my classmates and friends in Pittsburgh. They helped me get used to the study and life in Pittsburgh, and we shared a lot of happy moments together, which I would cherish for my whole life.

Finally, I would like to thank my husband, my parents and my parents-in-law for their selfless support and encouragement in my life as well as in my research. Without them, I would not be able to become a confident and grateful person I am now. Last but not the least, I want to say that my daughter, Claire, is the most precious gift I had during my PhD life. I also want to thank her for making me a proud mother.

1.0 INTRODUCTION

In this chapter, we describe important concepts that will be used frequently throughout the dissertation. We also describe the study that motivated this research. Finally, we provide a motivation and background for the research presented in subsequent chapters.

1.1 SEQUENTIALLY RANDOMIZED DESIGNS

Sequentially randomized designs are becoming common in biomedical research, particularly in clinical trials. These trials are usually designed to assess and compare the effects of different treatment regimes resulting from medical decision making at different stages of therapy. In a sequentially randomized clinical trial, eligible patients are first randomly assigned to receive one of the initial treatments. Patients meeting some criteria (e.g. no progressive diseases) are then randomized to receive one of the maintenance treatments. Usually, the procedure continues until all treatment options are exhausted. The basic structure of a two-stage randomization design is depicted in Figure 1. In this two-stage randomization design, patients are randomly assigned to J initial treatments, namely, A_1, A_2, ..., A_{J-1}, A_J. Then patients with a response (e.g. without progressive diseases) are re-randomized to K maintenance treatments, namely, B_1, B_2, ..., B_{K-1}, B_K, upon consent to further randomization.

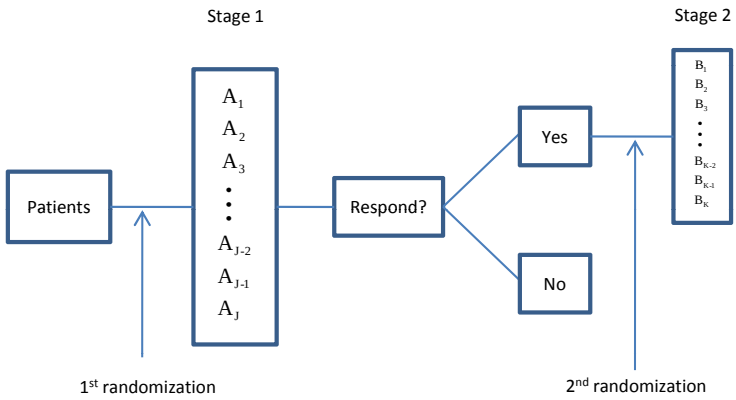

Figure 1: A conceptual framework of a two-stage randomization design.

1.2 DYNAMIC TREATMENT REGIMES

Dynamic treatment regimes are algorithms for assigning treatments to patients with complex diseases, where treatment consists of more than one episode of therapy, potentially with different dosages of the same agent or different agents. The multistage treatment assignment in sequentially randomized clinical trials results in dynamic treatment regimes consisting of initial treatment, intermediate response, and second stage treatment. A dynamic treatment regime in a two-stage treatment setting consists of an initial treatment, a decision rule for choosing the second-stage treatment, and the second-stage treatment. For example, in the setting described in Figure 1, a treatment regime could be "Treat with A_j (initial treatment), if patients respond and consent to further randomization, treat with B_k (second-stage treatment)". This is a dynamic treatment regime since the assignment of second-stage treatments depends on the intermediate outcome (response). We will denote the above regime by A_jB_k.

1.3 HIGH RISK NEUROBLASTOMA STUDY

Between 1991 and 1996, the Children's Cancer Group commenced a high risk neuroblastoma study aiming to assess whether a combination of myeloablative chemotherapy, total-body irradiation, and transplantation of autologous bone marrow purged of cancer cells (ABMT) improves event-free survival in children with high-risk neuroblastoma compared to intensive non-myeloablative chemotherapy, and to determine whether subsequent treatment with 13-cis-rectinoic acid (cis-RA) improves event-free survival further compared to no further therapy [13]. A two-stage randomization design was used for the treatment assignment. All patients were first treated with induction chemotherapy. Then 379 eligible patients without progressive diseases participated in the first-stage randomization, with 190 patients assigned to chemotherapy and 189 patients assigned to ABMT. A total of 176 patients either had progressive diseases or declined further randomization, so only 203 patients participated in the second stage randomization, with 102 patients assigned to cis-RA and 101 patients assigned to no further therapy. Thus, four possible treatment regimes could be constructed under the neuroblastoma study: (i) treat with chemotherapy followed by cis-RA if no progressive diseases present (CCR); (ii) treat with chemotherapy followed by no further therapy if no progressive diseases (CNR) present; (iii) treat with ABMT followed by cis-RA if no progressive diseases (ACR) present; (iv) treat with ABMT followed by no further therapy if no progressive diseases present (ANR). This formulation of dynamic treatment regimes from multistage treatment assignment allows simultaneous assessment of both first and second stage treatments, which has been the focus of such clinical trials.

1.4 MOTIVATION AND ORGANIZATION

Initial results from the outcome of the study was reported in Matthay et al. [13]. Using Kaplan-Meier procedure, probabilities of event-free survival beyond three years were estimated for both initial treatments ABMT and chemotherapy. A test of the significance of the differences in event-free survival at 3 years confirmed the superiority of ABMT

over chemotherapy alone. The study also compared cis-RA with no further therapy after chemotherapy or transplantation in improving the event-free survival among children with high-risk neuroblastoma. The difference in the event-free survival was statistically significant in favor of cis-RA therapy. In a follow up to their original publication, Matthay et al. [12] showed that ABMT significantly improves 5-year event-free survival and overall survival compared to non-myeloablative chemotherapy, and cis-RA provided after chemotherapy or transplantation significantly improves overall survival compared to no further therapy after consolidation.

However, the statistical analyses reported in these articles were not efficient and may have been inappropriate as well, since they did not take into account the information of those patients who had progressive disease or histologically confirmed disease before the second stage of treatment. Besides, the analyses only compared ABMT to chemotherapy alone ignoring subsequent randomization to cis-RA or no further therapy and compared cis-RA to no further therapy only among those who did not have progressive or histologically confirmed disease. Separate analyses for the first stage and second stage treatments may not be valid as they ignore the prior or post therapies received and the analysis is conditional on patients becoming eligible to receive second stage treatment [11].

There has been significant development in statistical methods for analyzing sequentially randomized designs (details are given in Sections 2.1 and 3.1). However, all the methods only apply to the comparisons of treatment regimes that share the same second stage therapy. In Chapter 2, We first propose to use accelerated failure time and proportional hazards models for estimating the effects of treatment regimes from sequentially randomized designs. Based on the proposed models, differences between treatment regimes in terms of their hazards are also tested. We investigate the properties of these methods and tests in a Monte Carlo simulation study. Finally the proposed models are applied to the long-term outcome of the high risk neuroblastoma study.

In Chapter 3, which is a follow-up study to the work presented in Chapter 2, we extend the proportional hazards model to a generalized Cox proportional hazards model that applies to comparisons of any combination of any number of treatment regimes regardless of the number of stages of treatment. Contrasts of dynamic treatment regimes are tested using

the Wald chi-square method. Both estimates and Wald chi-square tests of contrasts are evaluated through a simulation study. An application to a high risk neuroblastoma study complemented the earlier results reported on this study.

2.0 ACCELERATED FAILURE TIME AND PROPORTIONAL HAZARDS MODELS FOR SEQUENTIALLY RANDOMIZED DESIGNS

2.1 INTRODUCTION

The last decade has seen considerable advancement in the development of statistical methods for estimating the effects of dynamic treatment regimes [17, 15, 16, 11, 23, 24, 6, 5, 10]. Murphy et al. [17] developed marginal models for the mean response for a given dynamic treatment regime. In a follow-up article [15] they provided a methodology for constructing the optimal dynamic treatment regime. Lunceford et al. [11] proposed consistent survival and mean restricted survival estimators for treatment regimes in a two-stage randomization design. Wahed and Tsiatis [23, 24] introduced the most efficient estimator utilizing additional information from auxiliary variables. Guo and Tsiatis [5] derived a weighted risk set estimator (WRSE) on the basis of counting process theory [4] using a time-varying measurement for the intermediate response. Hernan et al. [6] described a simple method to compare dynamic treatment regimes via inverse probability weighting. Murphy and Bingham [16] used screening experiments to identify potential treatment components and screen out insignificant ones for developing dynamic treatment regimes.

Other articles focused on the comparisons of dynamic treatment regimes from two-stage randomization designs [10, 3]. Lokhnygina and Helterbrand [10] extended the Cox regression method to the estimation of log hazards of dynamic treatment regimes in a two-stage randomization design and applied a robust score test to compare two treatment regimes sharing the same second-stage treatment. Feng and Wahed [3] presented a modified supremum weighted log-rank test to test the equality of two dynamic treatment regimes. Both tests applied only to the comparisons of treatment regimes that share the same second-stage

therapy. In this article, we used accelerated failure time and proportional hazards models to derive the survival estimators for dynamic treatment regimes. Based on the proposed models, we also tested the equality of two survival distributions for any pairs of treatment regimes.

This chapter is organized as follows. In Section 2.2, we introduce the notation and assumptions. In Section 2.3, we describe the methods proposed for estimating the survival quantities and for comparing different treatment regimes based on the overall survival. In Section 2.4, a Monte Carlo simulation study is carried out to examine the performance of the proposed models. In Section 2.5, we analyze the high risk neuroblastoma dataset to compare overall survival for different neuroblastoma treatment regimes.

2.2 NOTATION AND ASSUMPTIONS

The basic structure of a two-stage randomization design is depicted in Figure 1, which reflects the design of the high risk neuroblastoma study described in brief in Section 2.1 (details are given in Section 2.5). In this two-stage randomization design, patients are randomly assigned to J initial treatments, namely, A_1, A_2, ..., A_{J-1}, A_J. Then patients with a response (e.g. without progressive diseases) are re-randomized to K maintenance treatments, namely, B_1, B_2, ..., B_{K-1}, B_K, upon consent to further randomization. A dynamic treatment regime in a two-stage treatment setting consists of an initial treatment, a decision rule for choosing the second-stage treatment, and the second-stage treatment. For example, in the setting described in Figure 1, a treatment regime could be "Treat with A_j (initial treatment), if patients respond and consent to further randomization, treat with B_k (second-stage treatment)". This is a dynamic treatment regime since the assignment of second-stage treatments depends on the intermediate outcome (response). We will denote the above regime by A_jB_k. The goal is to estimate survival quantities (e.g. hazards, survival probabilities) under various regimes and compare their effects. To facilitate this we resort to the idea of counterfactual variables from the causal inference literature. Although we are not particularly interested in the causal inference, this formulation will help us develop methods

to serve our goal.

Assume that the ith individual has a set of potential outcomes or counterfactuals [7]

$$\left\{R^*_{ji}, T^*_{j0i}, T^*_{jki}, j = 1, ..., J, k = 1, ..., K\right\},$$

where R^*_{ji} is the potential intermediate response for the ith patient were he/she assigned A_j as the initial treatment; T^*_{j0i} is the potential survival time for the ith patient if he/she were on A_j as the initial therapy, and did not respond; and T^*_{jki} indicates the potential survival time for the ith patient if he/she were on A_j as the initial therapy, responded and was consequently assigned B_k as the maintenance therapy. Then by definition, the overall survival for the ith patient under treatment regime A_jB_k can be written as

$$T_{jki} = (1 - R^*_{ji})T^*_{j0i} + R^*_{ji}T^*_{jki}.$$

In terms of these survival quantities, we define the hazard

$$\lambda_{A_jB_k}(t) = \lim_{\Delta t \to\ 0} \frac{P(t < T_{jk} < t + \Delta t)}{P(T_{jk} > t)\Delta t},$$

and the corresponding survival function $S_{A_jB_k}(t) = P(T_{jk} > t)$. Note that for a given individual i, not all JK survival times $T_{jki}, j = 1, ..., J, k = 1, ..., K$ can be observed, since in practice, a patient i cannot receive all treatment sequences. In fact, the observed data from a two-stage randomization design can be expressed as

$$\{X_{ji}, R_i, R_iZ_{ki}, U_i, \Delta_i\},$$

where

X_{ji} is the indicator for jth initial treatment, $X_{ji} = 1$ if the ith patient was assigned to A_j as initial treatment, and $X_{ji} = 0$ if otherwise;

R_i is the indicator for response and consent, $R_i = 1$ if the ith patient responded to the initial treatment and consent to further randomization, and $R_i = 0$ if otherwise;

$Z_{ki} = 1$ if the ith patient was assigned to B_k as maintenance treatment, and $Z_{ki} = 0$ if otherwise (note that Z_{ki} is defined only when $R_i = 1$);

and U_i denotes the observed death ($\Delta_i = 1$) or censoring time ($\Delta_i = 0$). In other words, when $\Delta_i = 1$, $U_i = T_i$, the potential survival time, and when $\Delta_i = 0$, $U_i = C_i$, the potential

censoring time. We assume that censoring is independent of observed data and counterfactuals. Patients who were censored without a response were treated as nonresponders (since a response was not observed before being censored; see Lunceford et al. [11]).

In order to draw inferences on counterfactual variables $T_{jk}, j = 1, ..., J, k = 1, ..., K$, one needs to make certain assumptions about the relationship between counterfactual and observed data. The first assumption is the consistency assumption [1], which could be described in statistical terms as

$$R_i = \sum_{j=1}^{J} X_{ji} R^*_{ji},$$

and

$$T_i = \sum_{j=1}^{J} \left\{ X_{ji} \left[(1 - R^*_{ji}) T^*_{j0i} + R^*_{ji} \left(\sum_{k=1}^{K} Z_{ki} T^*_{jki} \right) \right] \right\}. \tag{2.1}$$

In words, in the absence of censoring, the observed response and survival time for the ith patient equal his/her potential response and survival time under his/her observed treatment assignments. For example, if the ith patient was assigned to A_3 as initial treatment, responded and was consequently assigned to B_5 as maintenance treatment, then the observed survival time for the ith patient is equal to the potential survival time under treatment regime A_3B_5, namely, $T_i = T_{35i} = T^*_{35i}$. The other assumption is the "No unmeasured confounder" assumption. Briefly, patients with various treatment assignments have the equal distribution of potential outcomes [1]. This assumption can be expressed statistically as $P(X_j = 1|T_{jk}, j = 1, ..., J, k = 1, ..., K) = P(X_j = 1)$, and $P(Z_k = 1|R = 1, T_{jk}, j = 1, ..., J, k = 1, ..., K) = P(Z_k = 1|R = 1)$. Denote π_{Z_k} to be the probability of a patient being assigned to maintenance treatment B_k given that the patient responded to the initial treatment, namely, $\pi_{Z_k} = P(Z_k = 1|R = 1)$. In further developments, this will be assumed known, since the assignment is done through randomization.

2.3 METHODS

Our goal is to find the survival and hazard estimators for the treatment regimes A_jB_k, and also provide contrasts for comparing regimes A_jB_k, $j = 1, ..., J$ and $k = 1, ..., K$ based on the overall survival. Define $\lambda_{jk}(t)$ and $S_{jk}(t)$ to be the hazard and survival functions respectively corresponding to the counterfactual variable $T^*_{jk}, j = 1, ..., J; k = 0, 1, ...K$, then the hazard function $\lambda_{A_jB_k}(t)$ of the treatment regime A_jB_k can be expressed in terms of $\lambda_{jk}(t)$ and $S_{jk}(t)$, $j = 1, ..., J; k = 0, 1, ..., K$ as follows:

$$
\begin{aligned}
\lambda_{A_jB_k}(t) &= \lim_{\Delta t \to 0} \frac{P\left(t < T_{jk} < t + \Delta t\right)}{P\left(T_{jk} > t\right)\Delta t} \\
&= \lim_{\Delta t \to 0} \frac{P\left(t < T^*_{jk} < t + \Delta t | R = 1\right) P(R = 1) + P\left(t < T^*_{j0} < t + \Delta t | R = 0\right) P(R = 0)}{\left[P\left(T^*_{jk} > t | R = 1\right) P(R = 1) + P\left(T^*_{j0} > t | R = 0\right) P(R = 0)\right]\Delta t} \\
&= \lim_{\Delta t \to 0} \frac{P\left(t < T^*_{jk} < t + \Delta t\right)\pi_j + P\left(t < T^*_{j0} < t + \Delta t\right)(1 - \pi_j)}{\left[P\left(T^*_{jk} > t\right)\pi_j + P\left(T^*_{j0} > t\right)(1 - \pi_j)\right]\Delta t} \\
&= \frac{P\left(T^*_{jk} > t\right) P\left(T^*_{j0} > t\right)}{P\left(T^*_{jk} > t\right)\pi_j + P\left(T^*_{j0} > t\right)(1 - \pi_j)} \\
&\quad \lim_{\Delta t \to 0} \left\{ \frac{P\left(t < T^*_{jk} < t + \Delta t\right)}{P\left(T^*_{jk} > t\right)\Delta t} \frac{\pi_j}{P\left(T^*_{j0} > t\right)} + \frac{P\left(t < T^*_{j0} < t + \Delta t\right)}{P\left(T^*_{j0} > t\right)\Delta t} \frac{1 - \pi_j}{P\left(T^*_{jk} > t\right)} \right\} \\
&= \frac{P\left(T^*_{jk} > t\right)\pi_j}{P\left(T^*_{jk} > t\right)\pi_j + P\left(T^*_{j0} > t\right)(1 - \pi_j)} \lim_{\Delta t \to 0} \frac{P\left(t < T^*_{jk} < t + \Delta t\right)}{P\left(T^*_{jk} > t\right)\Delta t} \\
&\quad + \frac{P\left(T^*_{j0} > t\right)(1 - \pi_j)}{P\left(T^*_{jk} > t\right)\pi_j + P\left(T^*_{j0} > t\right)(1 - \pi_j)} \lim_{\Delta t \to 0} \frac{P\left(t < T^*_{j0} < t + \Delta t\right)}{P\left(T^*_{j0} > t\right)\Delta t} \\
&= \frac{P\left(T^*_{jk} > t\right)\pi_j\lambda_{jk}(t)}{P\left(T^*_{jk} > t\right)\pi_j + P\left(T^*_{j0} > t\right)(1 - \pi_j)} + \frac{P\left(T^*_{j0} > t\right)(1 - \pi_j)\lambda_{j0}(t)}{P\left(T^*_{jk} > t\right)\pi_j + P\left(T^*_{j0} > t\right)(1 - \pi_j)} \\
&= \frac{P\left(T^*_{jk} > t\right)\pi_j\lambda_{jk}(t) + P\left(T^*_{j0} > t\right)(1 - \pi_j)\lambda_{j0}(t)}{P\left(T^*_{jk} > t\right)\pi_j + P\left(T^*_{j0} > t\right)(1 - \pi_j)} \\
&= \frac{\pi_j S_{jk}(t)\lambda_{jk}(t) + (1 - \pi_j) S_{j0}(t)\lambda_{j0}(t)}{\pi_j S_{jk}(t) + (1 - \pi_j) S_{j0}(t)},
\end{aligned}
$$

where π_j is the probability of response for patients assigned to A_j as initial treatment expressed as $\pi_j = P(R = 1|X_j = 1)$. As an example, let $J = 2$ and $K = 2$, then the hazards

under regimes A_1B_1, A_1B_2, A_2B_1 and A_2B_2 can be written as

$$\lambda_{A_1B_1}(t) = \frac{\pi_1 S_{11}(t)\lambda_{11}(t) + (1-\pi_1)\, S_{10}(t)\lambda_{10}(t)}{\pi_1 S_{11}(t) + (1-\pi_1)\, S_{10}(t)}, \tag{2.2}$$

$$\lambda_{A_1B_2}(t) = \frac{\pi_1 S_{12}(t)\lambda_{12}(t) + (1-\pi_1)\, S_{10}(t)\lambda_{10}(t)}{\pi_1 S_{12}(t) + (1-\pi_1)\, S_{10}(t)}, \tag{2.3}$$

$$\lambda_{A_2B_1}(t) = \frac{\pi_2 S_{21}(t)\lambda_{21}(t) + (1-\pi_2)\, S_{20}(t)\lambda_{20}(t)}{\pi_2 S_{21}(t) + (1-\pi_2)\, S_{20}(t)}, \tag{2.4}$$

and

$$\lambda_{A_2B_2}(t) = \frac{\pi_2 S_{22}(t)\lambda_{22}(t) + (1-\pi_2)\, S_{20}(t)\lambda_{20}(t)}{\pi_2 S_{22}(t) + (1-\pi_2)\, S_{20}(t)}. \tag{2.5}$$

Corresponding survival functions of four treatment regimes are

$$S_{A_1B_1}(t) = \pi_1 S_{11}(t) + (1-\pi_1)\, S_{10}(t), \tag{2.6}$$

$$S_{A_1B_2}(t) = \pi_1 S_{12}(t) + (1-\pi_1)\, S_{10}(t), \tag{2.7}$$

$$S_{A_2B_1}(t) = \pi_2 S_{21}(t) + (1-\pi_2)\, S_{20}(t), \tag{2.8}$$

and

$$S_{A_2B_2}(t) = \pi_2 S_{22}(t) + (1-\pi_2)\, S_{20}(t). \tag{2.9}$$

Thus if one can estimate the probability of response and the survival and hazard functions $\lambda_{jk}(t)$ and $S_{jk}(t)$, then the above formulae can be used to estimate the hazard and survival functions for different regimes. The probability of response for patients assigned to A_j as initial treatment can be estimated by

$$\hat{\pi}_j = \frac{\sum X_{ji} R_i}{\sum X_{ji}}.$$

Nonparametric methods such as Nelson-Aalen (NA), semiparametric methods such as proportional hazards model (PHM), and parametric methods such as accelerated failure time model (AFTM) can be used to obtain the estimates of six survival functions [$S_{10}(t)$, $S_{20}(t)$,

$S_{11}(t)$, $S_{12}(t)$, $S_{21}(t)$, $S_{22}(t)$] and six hazard functions [$\lambda_{10}(t)$, $\lambda_{20}(t)$, $\lambda_{11}(t)$, $\lambda_{12}(t)$, $\lambda_{21}(t)$, $\lambda_{22}(t)$] from patients who actually received corresponding treatment sequences (see Sections 2.3.1-2.3.3).

After obtaining the six survival estimates, the survival functions of four treatment regimes can be easily obtained through $\hat{S}_{A_1B_1}(t) = \hat{\pi}_1\hat{S}_{11}(t) + (1-\hat{\pi}_1)\,\hat{S}_{10}(t)$, $\hat{S}_{A_1B_2}(t) = \hat{\pi}_1\hat{S}_{12}(t) + (1-\hat{\pi}_1)\,\hat{S}_{10}(t)$, $\hat{S}_{A_2B_1}(t) = \hat{\pi}_2\hat{S}_{21}(t) + (1-\hat{\pi}_2)\,\hat{S}_{20}(t)$, and $\hat{S}_{A_2B_2}(t) = \hat{\pi}_2\hat{S}_{22}(t) + (1-\hat{\pi}_2)\,\hat{S}_{20}(t)$. Similarly, one can obtain the estimates for the hazard functions from equations (2.2) - (2.5).

2.3.1 Nonparametric Methods

Based on the counting process notations described in Fleming and Harrington [4], the cumulative hazard rate for each subpopulation defined by the survival time T^*_{jk}, $j = 1, 2; k = 0, 1, 2$, can be estimated by the Nelson-Aalen estimator

$$\hat{\Lambda}_{jk}(t) = \int_0^t \frac{dN_{jk}(u)}{Y_{jk}(u)},$$

where $N_{jk}(u)$ is the event process for patients following the treatment path jk at time u (note that $k = 0$ indicates that the patient did not make it to the second stage of therapy),

$$N_{jk}(u) = \sum_{i=1}^{n} N_{jki}(u) = \sum_{i=1}^{n} I[U_i \le u, \Delta_i = 1, X_{ji} = 1, (1-R_i) + R_i Z_{ki} = 1],$$

and $Y_{jk}(u)$ is the number of individuals at risk at time u given by

$$Y_{jk}(u) = \sum_{i=1}^{n} I[U_i \ge u, X_{ji} = 1, (1-R_i) + R_i Z_{ki} = 1].$$

Then the corresponding hazard and survival functions can be estimated by $\hat{\lambda}_{jk}(t) = \frac{d\hat{\Lambda}_{jk}(t)}{dt}$ and $\hat{S}_{jk}(t) = \exp\{-\hat{\Lambda}_{jk}(t)\}$ respectively.

2.3.2 Semiparametric Methods

Let us assume that there are proportional hazards across different subpopulations defined by the survival times T^*_{jk}, $j = 1, 2; k = 0, 1, 2$, that is, the hazard ratio can be written as

$$\frac{\lambda_{jk}(t)}{\lambda_{j'k'}(t)} = e^{\gamma_{jkj'k'}}, \forall j \neq j' = 1, 2; k \neq k' = 0, 1, 2. \tag{2.10}$$

For simplicity, denote $\lambda_0(t)$ to be the hazard function for patients who were assigned to initial treatment A_1, responded and were assigned to maintenance treatment B_1, namely, $\lambda_0(t) = \lambda_{11}(t)$. Based on the proportional hazards model, the hazard functions $\lambda_{10}(t)$, $\lambda_{20}(t)$, $\lambda_{11}(t)$, $\lambda_{12}(t)$, $\lambda_{21}(t)$, and $\lambda_{22}(t)$ are equal to $\lambda_0(t)e^{\gamma_{1011}}$, $\lambda_0(t)e^{\gamma_{2011}}$, $\lambda_0(t)$, $\lambda_0(t)e^{\gamma_{1211}}$, $\lambda_0(t)e^{\gamma_{2111}}$, and $\lambda_0(t)e^{\gamma_{2211}}$ respectively.

The coefficient set under the proportional hazards model is estimated based on the partial likelihood function [2]. For details, see Therneau and Grambsch [22] Chapter 3. After fitting the model, the coefficient estimates $\hat{\gamma} = [\hat{\gamma}_{1011}, \hat{\gamma}_{2011}, \hat{\gamma}_{1211}, \hat{\gamma}_{2111}, \hat{\gamma}_{2211}]^T$ and their estimated variance covariance matrix $\hat{\Sigma}$ are obtained, as well as the Breslow's estimator of the baseline cumulative hazard function $\hat{\Lambda}_0(t)$ and the corresponding baseline hazard function $\hat{\lambda}_0(t) = \frac{d\hat{\Lambda}_0(t)}{dt}$. Thus, the six estimated survival functions $\hat{S}_{10}(t)$, $\hat{S}_{20}(t)$, $\hat{S}_{11}(t)$, $\hat{S}_{12}(t)$, $\hat{S}_{21}(t)$, and $\hat{S}_{22}(t)$ can be obtained as $\hat{S}_{10}(t) = \exp(-\hat{\Lambda}_0(t)e^{\hat{\gamma}_{1011}})$, $\hat{S}_{20}(t) = \exp(-\hat{\Lambda}_0(t)e^{\hat{\gamma}_{2011}})$, $\hat{S}_{11}(t) = \exp(-\hat{\Lambda}_0(t))$, $\hat{S}_{12}(t) = \exp(-\hat{\Lambda}_0(t)e^{\hat{\gamma}_{1211}})$, $\hat{S}_{21}(t) = \exp(-\hat{\Lambda}_0(t)e^{\hat{\gamma}_{2111}})$, and $\hat{S}_{22}(t) = \exp(-\hat{\Lambda}_0(t)e^{\hat{\gamma}_{2211}})$. Similarly, one can obtain the six estimated hazard functions as $\hat{\lambda}_{10}(t) = \hat{\lambda}_0(t)e^{\hat{\gamma}_{1011}}$, $\hat{\lambda}_{20}(t) = \hat{\lambda}_0(t)e^{\hat{\gamma}_{2011}}$, $\hat{\lambda}_{11}(t) = \hat{\lambda}_0(t)$, $\hat{\lambda}_{12}(t) = \hat{\lambda}_0(t)e^{\hat{\gamma}_{1211}}$, $\hat{\lambda}_{21}(t) = \hat{\lambda}_0(t)e^{\hat{\gamma}_{2111}}$, and $\hat{\lambda}_{22}(t) = \hat{\lambda}_0(t)e^{\hat{\gamma}_{2211}}$.

2.3.3 Parametric Methods

Under specific distributional assumptions about the shape of the survival function, we would be able to fit accelerated failure time models to different subpopulations defined by the survival times T^*_{jk}, $j = 1, 2; k = 0, 1, 2$ as

$$\ln T^*_{jk} = \mu_{jk} + \sigma_{jk} W.$$

A variety of distributions can be chosen for the survival time, such as Weibull distribution, log normal distribution, log logistic distribution, etc. We focus on the estimation for the Weibull distribution here for demonstration. Under the Weibull distributional assumption, the hazard and survival functions are given by

$$S_{jk}(t) = \exp(-\lambda_{jk} t^{\alpha_{jk}}),$$

and

$$\lambda_{jk}(t) = \lambda_{jk} \alpha t^{\alpha_{jk}-1},$$

where, in many instances, λ_{jk} and α_{jk} are reparametrized as $\lambda_{jk} = \exp(-\mu_{jk}/\sigma_{jk})$ and $\alpha_{jk} = 1/\sigma_{jk}$.

The estimates of the parameters μ_{jk} and σ_{jk} can be obtained through maximum likelihood method [8]. After fitting the Weibull distribution to the subpopulation, the estimates $\hat{\mu}_{jk}$ and $\hat{\sigma}_{jk}$, their respective estimated variance $\text{var}(\hat{\mu}_{jk})$ and $\text{var}(\hat{\sigma}_{jk})$, and their estimated covariance $\text{cov}(\hat{\mu}_{jk}, \hat{\sigma}_{jk})$ can be obtained. Then the maximum likelihood estimators of parameters λ_{jk} and α_{jk} are given by $\hat{\lambda}_{jk} = \exp(-\hat{\mu}_{jk}/\hat{\sigma}_{jk})$ and $\hat{\alpha}_{jk} = 1/\hat{\sigma}_{jk}$. Using the delta method, one can obtain the estimated variance of $\hat{\lambda}_{jk}$ and $\hat{\alpha}_{jk}$, and their estimated covariance as follows:

$$\text{var}(\hat{\lambda}_{jk}) = \exp\left(-2\frac{\hat{\mu}_{jk}}{\hat{\sigma}_{jk}}\right)\left[\frac{\text{var}(\hat{\mu}_{jk})}{\hat{\sigma}_{jk}^2} - 2\frac{\hat{\mu}_{jk}\text{cov}(\hat{\mu}_{jk}, \hat{\sigma}_{jk})}{\hat{\sigma}_{jk}^3} + \frac{\hat{\mu}_{jk}^2 \text{var}(\hat{\sigma}_{jk})}{\hat{\sigma}_{jk}^4}\right],$$

$$\text{var}(\hat{\alpha}_{jk}) = \frac{\text{var}(\hat{\sigma}_{jk})}{\hat{\sigma}_{jk}^4},$$

and

$$\text{cov}(\hat{\lambda}_{jk}, \hat{\alpha}_{jk}) = \exp\left(-\frac{\hat{\mu}_{jk}}{\hat{\sigma}_{jk}}\right)\left[\frac{\text{cov}(\hat{\mu}_{jk}, \hat{\sigma}_{jk})}{\hat{\sigma}_{jk}^3} - \frac{\hat{\mu}_{jk}\text{var}(\hat{\sigma}_{jk})}{\hat{\sigma}_{jk}^4}\right].$$

Therefore, the hazard and survival functions can be estimated as $\hat{\lambda}_{jk}(t) = \hat{\lambda}_{jk}\hat{\alpha}_{jk} t^{\hat{\alpha}_{jk}-1}$ and $\hat{S}_{jk}(t) = \exp(-\hat{\lambda}_{jk} t^{\hat{\alpha}_{jk}})$. Similarly, their estimated standard errors can be obtained using the delta method.

2.3.4 Treatment Regime Comparisons

Comparisons of treatment regimes in terms of their hazards can be carried out by integrating the weighted difference between two cumulative hazard functions [4]. For example, the Fleming-Harrington linear rank statistics for comparing cumulative hazard functions $\Lambda_{A_1B_1}(t)$ and $\Lambda_{A_2B_2}(t)$ is given by

$$\begin{aligned} W_{A_1B_1/A_2B_2} &= \int_0^\infty K_{A_1B_1/A_2B_2}(s)\left\{d\hat{\Lambda}_{A_1B_1}(t) - d\hat{\Lambda}_{A_2B_2}(t)\right\} \\ &= \int_0^\infty K_{A_1B_1/A_2B_2}(s)\left\{\hat{\lambda}_{A_1B_1}(s) - \hat{\lambda}_{A_2B_2}(s)\right\} ds, \end{aligned}$$

where the weight of K is chosen according to Feng and Wahed [3] as follows:

$$K_{A_1B_1/A_2B_2}(s) = \left\{\frac{n_{11}+n_{22}}{n_{11}n_{22}}\right\}^{\frac{1}{2}} \frac{\bar{Y}_{11}(s)\bar{Y}_{22}(s)}{\bar{Y}_{11}(s)+\bar{Y}_{22}(s)},$$

where $n_{jk}, j,k = 1,2$ is the total number of patients following the treatment path jk defined as $n_{jk} = \sum_{i=1}^n I[X_{ji} = 1, (1-R_i) + R_iZ_{ki} = 1]$; $\bar{Y}_{11}(s) = \sum_{i=1}^n W_{11i}I(U_i \geq s)$; $\bar{Y}_{22}(s) = \sum_{i=1}^n W_{22i}I(U_i \geq s)$; and $W_{jki}, j,k = 1,2$ is the weight function for the ith patient defined as $W_{jki} = X_{ji}(1-R_i) + X_{ji}R_iZ_{ki}/\pi_{Z_k}$. The test statistic $W_{A_1B_1/A_2B_2}$ is asymptotically normally distributed with mean 0 and some variance $\sigma^2_{W_{A_1B_1/A_2B_2}}$. We used a bootstrap resampling method to obtain the estimated variance $\hat{\sigma}^2_{W_{A_1B_1/A_2B_2}}$.

2.4 SIMULATION STUDY

A Monte-Carlo simulation study was conducted to evaluate the performance of all three methods described in Section 2.3: Nelson-Aalen (NA) estimator, proportional hazards model (PHM) and accelerated failure time model (AFTM). A simple two-stage randomization design was chosen for the simulation study. The indicator for the initial treatment A_1 (X_1) was sampled from $Bernoulli(0.5)$ distribution and the intermediate response (R) was drawn from $Bernoulli(0.5)$ to reflect the response rate in the neuroblastoma dataset. For the responders indicator for the maintenance treatment B_1 (Z_1) was generated from $Bernoulli(0.5)$. By

Table 1: Simulation scenarios

	Response Rate	Censoring Percentage	Responders	Nonresponders	True Survival Rates				
					t(year)	$S_{A_1B_1}(t)$	$S_{A_1B_2}(t)$	$S_{A_2B_1}(t)$	$S_{A_2B_2}(t)$
Scenario I	50%	30%	Weibull	Weibull	1	0.79	0.78	0.77	0.74
					3	0.54	0.51	0.55	0.50
					6	0.32	0.28	0.38	0.30
Scenario II	50%	30%	Log normal	Log normal	1	0.80	0.80	0.78	0.76
					3	0.48	0.48	0.54	0.48
					6	0.27	0.28	0.37	0.30
Scenario III	50%	30%	Log logistic	Log logistic	1	0.75	0.75	0.76	0.72
					3	0.42	0.43	0.52	0.43
					6	0.23	0.24	0.38	0.26
Scenario IV	50%	30%	Weibull	Log normal	1	0.79	0.77	0.77	0.75
					3	0.51	0.48	0.54	0.49
					6	0.31	0.27	0.38	0.31
Scenario V	50%	30%	Log normal	Log logistic	1	0.76	0.76	0.76	0.74
					3	0.45	0.45	0.51	0.46
					6	0.25	0.25	0.36	0.29

equation (2.1), the survival time for the ith patient under a simple two-stage randomization design can be expressed as

$$T_i = X_{1i}[(1-R_i)T^*_{10i} + R_i(Z_{1i}T^*_{11i} + Z_{2i}T^*_{12i})] + X_{2i}[(1-R_i)T^*_{20i} + R_i(Z_{1i}T^*_{21i} + Z_{2i}T^*_{22i})].$$

We generated $T^*_{jk},\ j = 1,2; k = 0,1,2$ from various distributions as described in Table 1. Under scenario I, the survival times T^*_{jk} were generated from Weibull distributions, more explicitly, $T^*_{jk},\ j = 1,2; k = 0,1,2$ was defined as

$$T^*_{jk} = \left\{ \frac{-\log(u_1)}{\lambda_{jk}} \right\}^{\frac{1}{\alpha_{jk}}}, \text{where } u_1 \sim Uniform(0,1).$$

Under scenario II, the survival times T^*_{jk} for each subpopulation followed log normal distributions, thus $T^*_{jk},\ j = 1,2; k = 0,1,2$ was defined as

$$T^*_{jk} = \exp\{\mu_{jk} + u_2 * \sigma_{jk}\}, \text{where } u_2 \sim Normal(0,1).$$

Under scenario III, the survival time T^*_{jk} for each subpopulation followed a log logistic distribution, thus $T^*_{jk},\ j = 1,2; k = 0,1,2$ was defined as

$$T^*_{jk} = \left\{ \frac{1/u_3 - 1}{\lambda_{jk}} \right\}^{\frac{1}{\alpha_{jk}}}, \text{where } u_3 \sim Uniform(0,1).$$

Under scenario IV, the survival times T^*_{jk}, $j = 1, 2; k = 1, 2$ (of responders) followed Weibull distributions, while the survival times T^*_{jk}, $j = 1, 2; k = 0$ (of nonresponders) followed log normal distributions. Under scenario V, the survival times T^*_{jk}, $j = 1, 2; k = 1, 2$ (of responders) followed log normal distributions, while the survival times T^*_{jk}, $j = 1, 2; k = 0$ (of nonresponders) followed log logistic distributions. Censoring time C was drawn from a uniform distribution, $Uniform(25, \tau)$, and τ was selected to achieve a censoring percentage of 30% approximately to reflect the censoring rate in the neuroblastoma dataset. For each scenario, 500 samples of size 400 were generated and a total of seven different models were fitted to each sample. These models represented the five mixture models presented in scenarios I to V above plus two others, one used Nelson-Aalen estimator to estimate the survival for subpopulations and the other used proportional hazards across subgroups (see Section 2.3). We used a bootstrap resampling method to obtain the variance estimator for the Fleming-Harrington linear rank statistic.

Simulation results are shown in Tables 2-3. Table 2 and Table 3 display the means of survival estimates, their estimated standard errors and coverages of probability of 95% confidence interval under scenarios I - V at different time points of 1-year and 3-year respectively. Since the survival data under scenario I were generated based on the Weibull distribution, the survival estimates obtained using the Weibull distribution performed very well, as one would expect, with the coverage probability close to 95% in most of the cases. Some of the survival estimates obtained using other parametric distributions, e.g. log normal distribution, were biased, and the coverage probability for one model was as low as 74.6%, which occurred for $S_{A_1B_2}(t)$ at 1-year for the log normal models. However, the estimates obtained using the log logistic distribution were unbiased, and the coverage probabilites were well-maintained. The coverage probabilities obatined using the PHM were relatively low at early time points, e.g. at 1-year, perhaps due to the smaller standard error estimates compared to other models. Furthermore, the survival estimates based on the NA estimator were unbiased with acceptable coverage probabilities, and the estimated standard errors were relatively larger compared to the ones we obtained using the other methods. Under scenario II, since the data were generated based on the log normal distribution, we observed unbiased survival estimates using the log normal distribution. Other parametric distributions also gave us

favorable coverage probabilities for the estimates except for the ones we obtained using the Weibull distribution. Survival estimates obtained using the PHM were noticeably biased at early time points, but the NA estimators performed very well, coverage probabilities being well-maintained. Under scenario III, the parametric methods (log normal distribution, log logistic distribution, and a combination of log normal and log logistic distribution) and NA estimators performed well, however, the other two parametric methods (Weibull distribution, and a combination of Weibull and log normal distribution) resulted biased estimates in most of the cases, and the PHM gave biased estimates at early time points. Under scenario IV, the data were generated based on a combination of Weibull and log normal distribution, therefore, we observed consistent coverage probabilites when the true distributions were fitted to the data. The estimates obtained using the NA estimator were also unbiased. However, all the other methods did not perform well, with some of the coverage probilities being smaller than 95%. Under scenario V, only the estimates calculated based on the Weibull distribution and the PHM were biased in some of the cases, but all the other methods provided us with favorable results. Thus, from the results we observed under scenario I - scenario V, it is clear that PHM does not perform well at early time points on the data generated based on any parametric distribution. However, NA estimator provides unbiased estimates under all true models, which is expected as NA estimator is unbiased in large samples. Moreover, the choice of distribution when fitting the AFTM affects the survival estimates to some extent.

Table 4 presents the rejection rates of the Fleming-Harrington tests based on all seven methods under scenario I - scenario V for 500 samples of size 400. A total of six null hypotheses $[H_1 : \lambda_{A_1B_1}(t) = \lambda_{A_1B_2}(t),\ H_2 : \lambda_{A_1B_1}(t) = \lambda_{A_2B_1}(t),\ H_3 : \lambda_{A_1B_1}(t) = \lambda_{A_2B_2}(t),$ $H_4 : \lambda_{A_1B_2}(t) = \lambda_{A_2B_1}(t),\ H_5 : \lambda_{A_1B_2}(t) = \lambda_{A_2B_2}(t),\ H_6 : \lambda_{A_2B_1}(t) = \lambda_{A_2B_2}(t)]$ were tested. Under scenario I, the rejection rates obtained using all the models were similar to each other. We also observed similar results under scenario II through scenario V. Under all the scenarios, the rejection rates obtained using the PHM and NA estimator were observed to be slightly smaller than the ones obtained using the parametric models in most of the cases. Thus, we would conclude that Fleming-Harrington test is robust regardless of the methods used to obtain the hazard and survival estimates. In conclusion, although survival estimates at specific time points varied somewhat across different methods (NA, PHM,

Table 2: Survival estimates (EST), standard errors (SE) in parentheses, and coverage probability of 95% confidence interval (CP) at t = 1 year under scenarios I - V based on samples of size 400 at 50% response rate and 30% censoring percentage. WEI: Weibull distributions, LN: Log normal distributions, LG: Log logistic distributions, WEILN: Weibull distributions for responders and log normal distributions for nonresponders, LNLG: Log normal distributions for responders and log logistic distributions for nonresponders, PHM: Proportional hazards model, NA: Nelson-Aalen Estimators

		A_1B_1		A_1B_2		A_2B_1		A_2B_2	
		EST (SE)	CP(%)	EST (SE)	CP(%)	EST (SE)	CP(%)	EST (SE)	CP(%)
Scenario I	WEI	0.79 (0.028)	95.8	0.78 (0.029)	94.2	0.77 (0.029)	94.6	0.75 (0.030)	94.6
	LN	0.76 (0.029)	79.2	0.74 (0.030)	74.6	0.73 (0.030)	79.0	0.71 (0.031)	75.0
	LG	0.79 (0.029)	93.6	0.78 (0.030)	92.0	0.76 (0.030)	93.4	0.74 (0.031)	93.0
	WEILN	0.77 (0.028)	89.2	0.75 (0.029)	86.0	0.74 (0.029)	85.2	0.72 (0.031)	86.6
	LNLG	0.78 (0.029)	90.2	0.76 (0.030)	89.2	0.75 (0.030)	91.0	0.72 (0.031)	88.4
	PHM	0.78 (0.026)	96.0	0.76 (0.027)	89.8	0.78 (0.026)	89.8	0.76 (0.028)	91.0
	NA	0.79 (0.033)	95.6	0.77 (0.034)	95.2	0.76 (0.034)	94.0	0.74 (0.035)	94.4

		A_1B_1		A_1B_2		A_2B_1		A_2B_2	
		EST (SE)	CP(%)	EST (SE)	CP(%)	EST (SE)	CP(%)	EST (SE)	CP(%)
Scenario II	WEI	0.80 (0.027)	97.4	0.80 (0.027)	97.8	0.79 (0.027)	93.8	0.78 (0.028)	93.8
	LN	0.80 (0.027)	94.0	0.80 (0.027)	94.4	0.78 (0.027)	93.6	0.76 (0.028)	95.0
	LG	0.80 (0.027)	93.6	0.80 (0.027)	94.2	0.79 (0.028)	94.4	0.77 (0.029)	93.8
	WEILN	0.79 (0.027)	96.0	0.79 (0.027)	96.4	0.78 (0.027)	95.0	0.76 (0.029)	96.2
	LNLG	0.80 (0.027)	92.4	0.80 (0.027)	93.2	0.79 (0.028)	93.2	0.77 (0.029)	94.0
	PHM	0.77 (0.026)	88.0	0.77 (0.026)	90.2	0.80 (0.026)	88.8	0.78 (0.027)	90.0
	NA	0.79 (0.032)	95.4	0.79 (0.032)	94.6	0.77 (0.032)	94.8	0.76 (0.034)	95.2

		A_1B_1		A_1B_2		A_2B_1		A_2B_2	
		EST (SE)	CP(%)	EST (SE)	CP(%)	EST (SE)	CP(%)	EST (SE)	CP(%)
Scenario III	WEI	0.75 (0.029)	96.6	0.76 (0.029)	96.4	0.77 (0.028)	93.2	0.74 (0.031)	93.2
	LN	0.74 (0.030)	91.6	0.74 (0.030)	92.0	0.75 (0.029)	93.6	0.71 (0.031)	92.8
	LG	0.75 (0.030)	94.8	0.75 (0.030)	94.8	0.76 (0.029)	95.2	0.73 (0.032)	94.2
	WEILN	0.74 (0.030)	95.0	0.74 (0.030)	95.2	0.75 (0.028)	95.4	0.72 (0.031)	96.0
	LNLG	0.74 (0.031)	94.0	0.75 (0.030)	93.6	0.76 (0.029)	93.4	0.72 (0.032)	92.2
	PHM	0.73 (0.029)	90.4	0.73 (0.028)	89.8	0.78 (0.027)	88.0	0.74 (0.029)	88.6
	NA	0.74 (0.035)	95.2	0.74 (0.035)	94.6	0.76 (0.033)	95.6	0.72 (0.036)	95.2

		A_1B_1		A_1B_2		A_2B_1		A_2B_2	
		EST (SE)	CP(%)	EST (SE)	CP(%)	EST (SE)	CP(%)	EST (SE)	CP(%)
Scenario IV	WEI	0.80 (0.028)	91.6	0.79 (0.028)	92.8	0.79 (0.028)	93.6	0.77 (0.029)	91.8
	LN	0.78 (0.028)	89.4	0.77 (0.029)	91.2	0.77 (0.028)	94.2	0.74 (0.030)	93.4
	LG	0.80 (0.028)	89.0	0.78 (0.029)	90.4	0.78 (0.029)	95.2	0.76 (0.031)	92.4
	WEILN	0.79 (0.028)	93.0	0.78 (0.029)	95.4	0.77 (0.028)	97.0	0.75 (0.029)	95.4
	LNLG	0.79 (0.029)	87.8	0.77 (0.030)	91.2	0.77 (0.029)	94.8	0.74 (0.031)	93.8
	PHM	0.77 (0.026)	93.2	0.75 (0.027)	90.2	0.79 (0.026)	90.4	0.76 (0.028)	91.6
	NA	0.78 (0.033)	93.6	0.77 (0.034)	94.8	0.77 (0.033)	96.2	0.74 (0.035)	95.8

		A_1B_1		A_1B_2		A_2B_1		A_2B_2	
		EST (SE)	CP(%)	EST (SE)	CP(%)	EST (SE)	CP(%)	EST (SE)	CP(%)
Scenario V	WEI	0.77 (0.028)	97.2	0.77 (0.028)	97.2	0.77 (0.028)	94.0	0.75 (0.029)	95.2
	LN	0.76 (0.028)	94.8	0.76 (0.028)	95.0	0.76 (0.028)	93.4	0.74 (0.030)	94.8
	LG	0.77 (0.029)	95.4	0.77 (0.029)	95.6	0.76 (0.029)	94.8	0.74 (0.030)	94.0
	WEILN	0.75 (0.029)	96.0	0.75 (0.029)	96.0	0.75 (0.028)	95.2	0.73 (0.030)	95.8
	LNLG	0.77 (0.029)	94.8	0.77 (0.029)	95.2	0.76 (0.029)	94.0	0.74 (0.030)	95.0
	PHM	0.74 (0.028)	90.2	0.74 (0.028)	92.6	0.78 (0.027)	89.0	0.75 (0.029)	92.6
	NA	0.76 (0.033)	94.8	0.76 (0.033)	95.4	0.75 (0.033)	95.6	0.74 (0.035)	95.2

Table 3: Survival estimates (EST), standard errors (SE) in parentheses, and coverage probability of 95% confidence interval (CP) at t = 3 year under scenarios I - V based on samples of size 400 at 50% response rate and 30% censoring percentage. WEI: Weibull distributions, LN: Log normal distributions, LG: Log logistic distributions, WEILN: Weibull distributions for responders and log normal distributions for nonresponders, LNLG: Log normal distributions for responders and log logistic distributions for nonresponders, PHM: Proportional hazards model, NA: Nelson-Aalen Estimators

		A_1B_1		A_1B_2		A_2B_1		A_2B_2	
		EST (SE)	CP(%)	EST (SE)	CP(%)	EST (SE)	CP(%)	EST (SE)	CP(%)
Scenario I	WEI	0.54 (0.037)	96.2	0.51 (0.037)	93.4	0.55 (0.037)	93.6	0.50 (0.037)	94.4
	LN	0.51 (0.037)	90.8	0.47 (0.037)	86.4	0.53 (0.037)	92.6	0.47 (0.038)	91.0
	LG	0.52 (0.039)	94.4	0.49 (0.039)	91.8	0.53 (0.038)	93.6	0.48 (0.039)	93.0
	WEILN	0.53 (0.037)	95.8	0.49 (0.037)	93.4	0.54 (0.037)	94.8	0.49 (0.037)	94.2
	LNLG	0.51 (0.038)	91.0	0.48 (0.038)	87.2	0.53 (0.037)	92.6	0.47 (0.038)	91.0
	PHM	0.53 (0.037)	96.0	0.50 (0.038)	93.2	0.55 (0.038)	94.2	0.50 (0.039)	93.4
	NA	0.54 (0.043)	94.2	0.50 (0.043)	93.0	0.54 (0.042)	93.8	0.49 (0.043)	93.6
		A_1B_1		A_1B_2		A_2B_1		A_2B_2	
		EST (SE)	CP(%)	EST (SE)	CP(%)	EST (SE)	CP(%)	EST (SE)	CP(%)
Scenario II	WEI	0.53 (0.037)	79.4	0.53 (0.037)	79.8	0.57 (0.036)	87.0	0.52 (0.037)	83.6
	LN	0.48 (0.037)	95.4	0.48 (0.037)	93.8	0.54 (0.037)	94.2	0.48 (0.037)	95.2
	LG	0.48 (0.039)	95.6	0.48 (0.039)	93.4	0.54 (0.038)	94.0	0.48 (0.039)	95.2
	WEILN	0.50 (0.037)	94.2	0.50 (0.037)	94.2	0.55 (0.037)	95.4	0.50 (0.037)	93.6
	LNLG	0.48 (0.038)	95.6	0.48 (0.038)	93.0	0.53 (0.037)	93.8	0.48 (0.038)	94.8
	PHM	0.47 (0.037)	95.2	0.47 (0.038)	93.0	0.53 (0.038)	96.4	0.48 (0.039)	94.6
	NA	0.48 (0.043)	95.2	0.48 (0.043)	94.4	0.53 (0.042)	93.4	0.48 (0.043)	94.6
		A_1B_1		A_1B_2		A_2B_1		A_2B_2	
		EST (SE)	CP(%)	EST (SE)	CP(%)	EST (SE)	CP(%)	EST (SE)	CP(%)
Scenario III	WEI	0.46 (0.038)	87.2	0.47 (0.038)	84.4	0.55 (0.037)	87.6	0.47 (0.038)	83.2
	LN	0.42 (0.038)	95.6	0.43 (0.038)	95.8	0.52 (0.037)	94.0	0.44 (0.038)	93.0
	LG	0.42 (0.039)	94.6	0.43 (0.039)	95.8	0.52 (0.038)	94.6	0.44 (0.039)	93.2
	WEILN	0.44 (0.038)	91.8	0.45 (0.038)	92.2	0.54 (0.037)	94.4	0.46 (0.038)	89.2
	LNLG	0.42 (0.038)	94.6	0.42 (0.038)	94.6	0.52 (0.037)	93.4	0.43 (0.038)	94.4
	PHM	0.41 (0.038)	94.0	0.42 (0.038)	94.2	0.52 (0.039)	93.8	0.44 (0.041)	93.4
	NA	0.42 (0.044)	91.0	0.42 (0.043)	92.6	0.52 (0.042)	93.8	0.43 (0.043)	94.2
		A_1B_1		A_1B_2		A_2B_1		A_2B_2	
		EST (SE)	CP(%)	EST (SE)	CP(%)	EST (SE)	CP(%)	EST (SE)	CP(%)
Scenario IV	WEI	0.53 (0.037)	89.6	0.50 (0.037)	91.0	0.56 (0.036)	92.2	0.51 (0.037)	91.0
	LN	0.49 (0.037)	91.4	0.46 (0.037)	92.0	0.53 (0.037)	94.6	0.47 (0.037)	93.8
	LG	0.50 (0.039)	92.6	0.47 (0.039)	93.6	0.53 (0.038)	95.4	0.48 (0.039)	94.4
	WEILN	0.51 (0.037)	93.2	0.48 (0.037)	94.6	0.54 (0.037)	95.6	0.49 (0.037)	95.6
	LNLG	0.49 (0.038)	89.2	0.45 (0.038)	90.0	0.52 (0.037)	93.8	0.47 (0.038)	91.8
	PHM	0.50 (0.038)	93.2	0.47 (0.038)	94.4	0.54 (0.038)	95.6	0.49 (0.039)	96.0
	NA	0.51 (0.043)	93.8	0.48 (0.044)	94.6	0.53 (0.042)	95.0	0.49 (0.043)	95.4
		A_1B_1		A_1B_2		A_2B_1		A_2B_2	
		EST (SE)	CP(%)	EST (SE)	CP(%)	EST (SE)	CP(%)	EST (SE)	CP(%)
Scenario V	WEI	0.49 (0.037)	79.6	0.49 (0.037)	80.6	0.55 (0.037)	86.2	0.50 (0.037)	85.8
	LN	0.45 (0.037)	94.8	0.45 (0.037)	95.0	0.52 (0.037)	95.0	0.47 (0.038)	95.0
	LG	0.45 (0.039)	95.6	0.45 (0.039)	95.0	0.52 (0.038)	95.4	0.46 (0.039)	93.6
	WEILN	0.47 (0.038)	91.0	0.47 (0.037)	90.6	0.53 (0.037)	92.4	0.48 (0.038)	92.2
	LNLG	0.45 (0.038)	95.8	0.45 (0.038)	95.4	0.51 (0.037)	95.6	0.46 (0.038)	94.4
	PHM	0.43 (0.038)	93.8	0.43 (0.038)	95.2	0.51 (0.039)	93.4	0.46 (0.040)	95.8
	NA	0.44 (0.043)	91.6	0.44 (0.043)	94.0	0.51 (0.042)	94.0	0.45 (0.043)	93.6

Table 4: The rejection rates of Fleming-Harrington tests under scenario I-V based on samples of size 400 at 50% response rate and 30% censoring percentage. $H_1 : \lambda_{A_1B_1}(t) = \lambda_{A_1B_2}(t)$, $H_2 : \lambda_{A_1B_1}(t) = \lambda_{A_2B_1}(t)$, $H_3 : \lambda_{A_1B_1}(t) = \lambda_{A_2B_2}(t)$, $H_4 : \lambda_{A_1B_2}(t) = \lambda_{A_2B_1}(t)$, $H_5 : \lambda_{A_1B_2}(t) = \lambda_{A_2B_2}(t)$, $H_6 : \lambda_{A_2B_1}(t) = \lambda_{A_2B_2}(t)$, WEI: Weibull distributions, LN: Log normal distributions, LG: Log logistic distributions, WEILN: Weibull distributions for responders and log normal distributions for nonresponders, LNLG: Log normal distributions for responders and log logistic distributions for nonresponders, PHM: Proportional hazards model, NA: Nelson-Aalen Estimators

		H_1	H_2	H_3	H_4	H_5	H_6
Scenario I	WEI	0.174	0.098	0.090	0.280	0.060	0.298
	LN	0.156	0.084	0.090	0.268	0.062	0.290
	LG	0.152	0.088	0.084	0.280	0.064	0.286
	WEILN	0.164	0.090	0.088	0.284	0.064	0.284
	LNLG	0.156	0.092	0.086	0.270	0.060	0.292
	PHM	0.152	0.104	0.076	0.294	0.054	0.280
	NA	0.174	0.090	0.086	0.246	0.064	0.270

		H_1	H_2	H_3	H_4	H_5	H_6
Scenario II	WEI	0.062	0.300	0.066	0.286	0.046	0.284
	LN	0.066	0.318	0.066	0.284	0.042	0.282
	LG	0.070	0.322	0.062	0.288	0.044	0.286
	WEILN	0.062	0.302	0.062	0.282	0.042	0.276
	LNLG	0.066	0.308	0.064	0.284	0.042	0.282
	PHM	0.060	0.310	0.066	0.282	0.044	0.278
	NA	0.060	0.234	0.064	0.232	0.056	0.274

		H_1	H_2	H_3	H_4	H_5	H_6
Scenario III	WEI	0.074	0.632	0.088	0.550	0.078	0.542
	LN	0.070	0.622	0.080	0.542	0.070	0.538
	LG	0.076	0.628	0.092	0.548	0.070	0.548
	WEILN	0.076	0.630	0.084	0.540	0.076	0.546
	LNLG	0.070	0.624	0.086	0.546	0.070	0.538
	PHM	0.060	0.618	0.078	0.546	0.076	0.502
	NA	0.074	0.428	0.064	0.412	0.060	0.520

		H_1	H_2	H_3	H_4	H_5	H_6
Scenario IV	WEI	0.160	0.172	0.062	0.422	0.080	0.308
	LN	0.148	0.152	0.054	0.390	0.066	0.304
	LG	0.134	0.152	0.054	0.376	0.070	0.280
	WEILN	0.160	0.174	0.062	0.424	0.074	0.308
	LNLG	0.152	0.160	0.054	0.382	0.070	0.300
	PHM	0.152	0.164	0.038	0.440	0.062	0.284
	NA	0.154	0.144	0.048	0.296	0.066	0.254

		H_1	H_2	H_3	H_4	H_5	H_6
Scenario V	WEI	0.068	0.384	0.076	0.374	0.072	0.304
	LN	0.070	0.382	0.074	0.378	0.074	0.302
	LG	0.074	0.398	0.074	0.376	0.070	0.298
	WEILN	0.072	0.370	0.080	0.364	0.072	0.304
	LNLG	0.070	0.374	0.070	0.374	0.068	0.300
	PHM	0.054	0.372	0.068	0.364	0.060	0.290
	NA	0.060	0.288	0.068	0.284	0.066	0.294

AFTM), Fleming-Harrington test of difference in survival/hazard curves between two treatment regimes provided very similar conclusions.

2.5 ANALYSIS OF NEUROBLASTOMA DATASET

A high risk neuroblastoma study was conducted by the Children's Cancer Group between 1991 and 1996 with the goal of assessing whether a combination of myeloablative chemotherapy, total-body irradiation, and transplantation of autologous bone marrow purged of cancer cells (ABMT) improves event-free survival in children with high-risk neuroblastoma compared to intensive non-myeloablative chemotherapy, and to determine whether subsequent treatment with 13-cis-rectinoic acid (cis-RA) improves event-free survival further compared to no further therapy [13]. A two-stage randomization design was used for the treatment assignment. All patients were first treated with induction chemotherapy. Then 379 eligible patients without progressive diseases participated in the first-stage randomization, with 190 patients assigned to chemotherapy and 189 patients assigned to ABMT. A total of 176 patients either had progressive diseases or declined further randomization, so only 203 patients participated in the second stage randomization, with 102 patients assigned to cis-RA and 101 patients assigned to no further therapy. The initial outcome from the neuroblastoma study was analyzed in Matthay et al. [13]. Matthay et al. [12] reported the long-term study results. However, both articles separately compared chemotherapy to ABMT, and cis-RA to no further therapy among those who participated in the second randomization. Such analyses separated the first and second stage treatments and ignored the information from those patients who had progressive diseases or declined further randomization, leading to inefficient use of data.

As described before, there are four possible treatment regimes in this data, namely, CCR, CNR, ACR, and ANR (see Section 2.1). We first identified the 6 subgroups in the data: patients who were assigned to chemotherapy as initial treatment and did not respond; patients who were assigned to chemotherapy as initial treatment, responded and were assigned to cis-RA as maintenance treatment; patients who were assigned to chemotherapy as initial

Table 5: AIC values for a total of 18 models fitted to the neuroblastoma dataset

Initial Therapy	Response	Second-stage Therapy	Weibull	Log Logistic	Log Normal
Chemotherapy	No		1109.55	1192.78	1092.47
ABMT	No		1173.84	1278.44	1154.31
Chemotherapy	Yes	cis-RA	618.84	655.84	608.46
Chemotherapy	Yes	No Further Therapy	619.04	653.88	609.86
ABMT	Yes	cis-RA	415.74	446.31	409.72
ABMT	Yes	No Further Therapy	486.77	521.44	479.38

treatment, responded and were assigned to no further therapy; and three other equivalent subgroups corresponding to those who were assigned to ABMT as initial treatment.

For each subgroup we first computed the survival curve using the NA estimator. Based on these estimates we obtained the survival curves for the four regimes through the formulae (2.6)-(2.9) described in Section 2.3. The overall survival curves for these four treatment regimes (CCR, CNR, ACR, ANR) are shown in Figure 2(a). The survival curves were close to each other early into the study, but deviated at later times. We then fitted the PHM to the neuroblastoma data as laid out in Section 2.3 and obtained the estimated survival curves for the four treatment regimes. The survival curves are depicted in Figure 2(b). The three survival curves for treatment regimes CCR, CNR, and ANR followed each other, while the survival curve for ACR was almost always higher compared to other regimes. Finally we fitted AFTMs to estimate the subgroup-specific survival functions. For each subgroup, we fitted Weibull, log logistic and log normal distributions and chose the best model with the lowest Akaike information criterion (AIC). Table 5 presents the AICs for a total of 18 models involved. It was observed that the AIC was minimum when the log normal distribution was used as the parametric model for all six subgroups. Figure 2(c) shows the corresponding overall survival curves for the four treatment regimes. The pattern follows that of the curves obtained by fitting the PHM. At the late stage of the study, the survival curve for treatment regime ACR seemed to differ somewhat from the other three survival curves (CCR, CNR, ANR), while the overall survival curves for treatment regimes CCR, CNR, and ANR followed

each other closely. The estimated variance for survival estimates were obtained through a bootstrap resampling method in both the NA estimator and PHM, however, we employed delta method for the AFTMs. Figure 3 compares all three methods for all four regimes. The survival curves from the NA estimator, PHM and AFTM were similar to each other, with small deviations at specific time points. Under the four treatment regimes, the survival estimates from the AFTM were always slightly larger than the other two during the first five years of the study, but decreased rapidly afterwards.

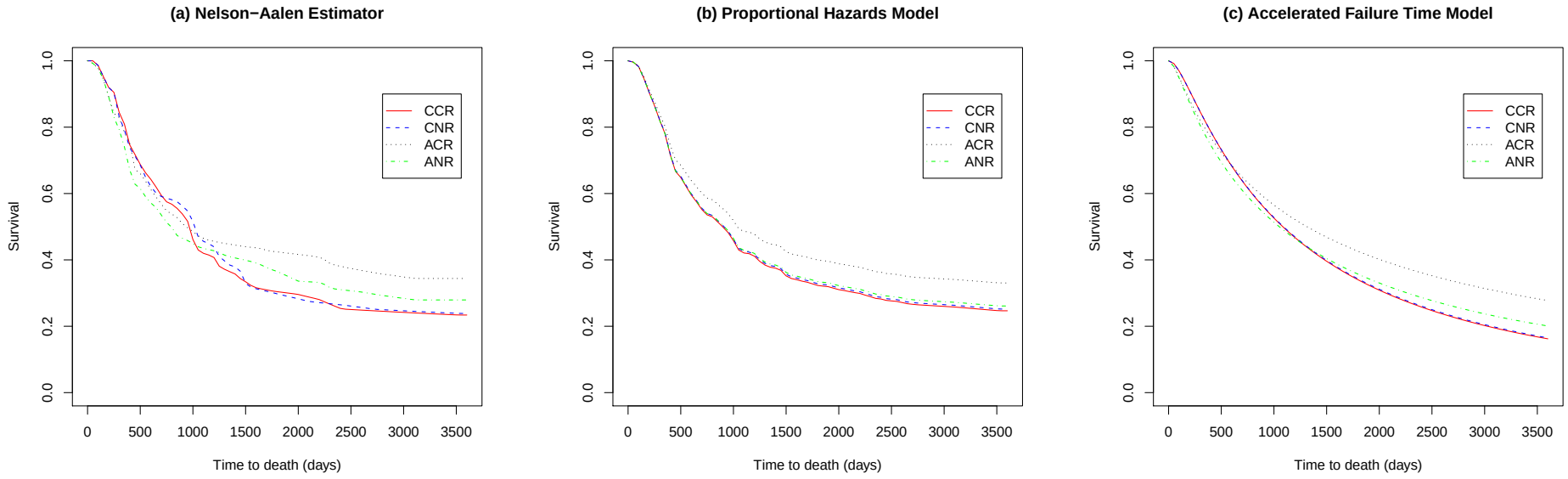

Figure 2: Overall survival curves under four treatment regimes in the neuroblastoma study. CCR: "treat with chemotherapy followed by cis-RA if no progressive disease", CNR: "treat with chemotherapy followed by no further therapy if no progressive disease", ACR: "treat with ABMT followed by cis-RA if no progressive disease", ANR: "treat with ABMT followed by no further therapy if no progressive disease"

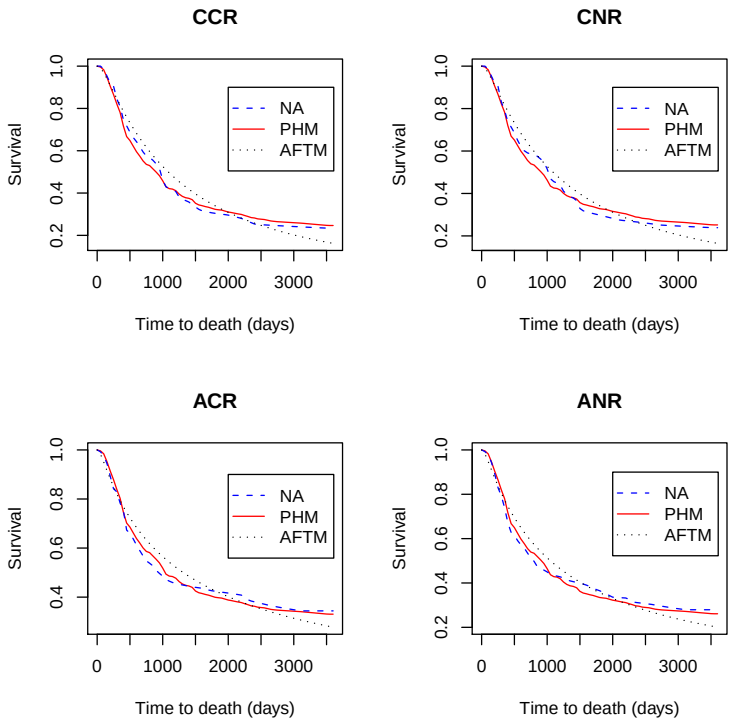

Figure 3: Comparisons of three methods for four treatment regimes in the neuroblastoma study. CCR: "treat with chemotherapy followed by cis-RA if no progressive disease", CNR: "treat with chemotherapy followed by no further therapy if no progressive disease", ACR: "treat with ABMT followed by cis-RA if no progressive disease", ANR: "treat with ABMT followed by no further therapy if no progressive disease" PHM: "Proportional Hazards Model", NA: "Nelson-Aalen Estimator", AFTM: "Accelerated Failure Time Model"

We performed comparisons of treatment regimes using the NA estimator, PHM and AFTM respectively. A total of six different hypotheses comparing pairwise treatment regimes were tested using the Fleming-Harrington two-sample test. The results are shown in Table 6. For simplicity, only first three tests would be described in details. First of all, we tested if there was a significant difference in the hazards of treatment regimes sharing the same initial treatment of "chemotherapy." The null hypothesis can be described as $H_1 : \lambda_{CCR}(t) = \lambda_{CNR}(t)$. The tests resulted in p-values equal to 0.50, 0.90 and 0.96 for the NA estimator, PHM and AFTM respectively, showing that there was no statistically significant difference in the hazards of treatment regimes sharing the same initial treatment of "chemotherapy." Thus, patients assigned to initial treatment of "chemotherapy" and then assigned to "cis-RA" upon response had similar survival compared to those assigned to "no further therapy" upon response to initial treatment of "chemotherapy."

Secondly, we tested if there was a significant difference in the hazards of treatment regimes sharing the same maintenance treatment of "cis-RA." The tests of the null hypothesis $H_2 : \lambda_{CCR}(t) = \lambda_{ACR}(t)$ resulted in p-values of 0.22, 0.22 and 0.25 for the NA estimator, PHM and AFTM respectively. This implied that the null hypothesis would not be rejected at $\alpha = 0.5$. Therefore, we would conclude that for patients who were assigned to "cis-RA" as maintenance treatment upon response, there was no significant difference in the overall survival between those who were assigned to "chemotherapy" and those who were assigned to "ABMT" as initial treatment.

The hypothesis that there was no significant difference in the hazards of treatment regimes with different initial treatments and different maintenance treatments was then tested using $H_3 : \lambda_{CCR}(t) = \lambda_{ANR}(t)$. The hazards of CCR and ANR were not statistically significantly different with the p-values being 0.86, 0.87 and 0.91 for the NA estimator, PHM and AFTM respectively, implying that there was no difference in the overall survival for patients who were assigned to "chemotherapy" as initial therapy and "cis-RA" as maintenance therapy upon response and for those who were assigned to "ABMT" as initial therapy and "no further therapy" as maintenance therapy upon response. Other pairwise comparisons were not statistically significant.

Table 6: Fleming-Harrington test results for the neuroblastoma dataset. CCR: "treat with chemotherapy followed by cis-RA if no progressive disease", CNR: "treat with chemotherapy followed by no further therapy if no progressive disease", ACR: "treat with ABMT followed by cis-RA if no progressive disease", ANR: "treat with ABMT followed by no further therapy if no progressive disease", $H_1 : \lambda_{CCR}(t) = \lambda_{CNR}(t)$, $H_2 : \lambda_{CCR}(t) = \lambda_{ACR}(t)$, $H_3 : \lambda_{CCR}(t) = \lambda_{ANR}(t)$, $H_4 : \lambda_{CNR}(t) = \lambda_{ACR}(t)$, $H_5 : \lambda_{CNR}(t) = \lambda_{ANR}(t)$, $H_6 : \lambda_{ACR}(t) = \lambda_{ANR}(t)$

	Nelson-Aalen Estimator		
	Test Statistic	Standard Error	P-value
H_1	0.73	1.078	0.50
H_2	1.72	1.390	0.22
H_3	0.27	1.491	0.86
H_4	1.08	1.245	0.39
H_5	-0.31	1.337	0.82
H_6	-1.37	1.038	0.19
	Proportional Hazards Model		
	Test Statistic	Standard Error	P-value
H_1	0.13	1.049	0.90
H_2	1.65	1.354	0.22
H_3	0.22	1.371	0.87
H_4	1.54	1.260	0.22
H_5	0.10	1.272	0.94
H_6	-1.37	1.053	0.19
	Accelerated Failure Time Model *		
	Test Statistic	Standard Error	P-value
H_1	0.06	1.164	0.96
H_2	1.59	1.373	0.25
H_3	0.17	1.409	0.91
H_4	1.55	1.254	0.22
H_5	0.12	1.293	0.93
H_6	-1.34	1.068	0.21

* Log normal model for each subgroup.

3.0 COX PROPORTIONAL HAZARDS MODEL FOR COMPARING DYNAMIC TREATMENT REGIMES WITH TIME DEPENDENT INTERMEDIATE RESPONSE

3.1 INTRODUCTION

Recently, there has been significant improvement in statistical methods for analyzing sequentially randomized designs [17, 11, 15, 23, 5, 24, 10]. Many of these articles use the idea of dynamic treatment regimes to analyze the data simultaneously from both stages. Multistage treatment assignment results in dynamic treatment regimes consisting of initial treatments, intermediate responses and second stage treatments. For example, one dynamic regime in the high risk neuroblastoma study could be defined as: "Treat with ABMT followed by chemotherapy, if the disease remains stable, treat with cis-RA". Such formulation of dynamic treatment regimes from multistage treatment assignment allows simultaneous assessment of both first and second stage treatments. For instance, one could compare the above regime to a regime that follows ABMT after chemotherapy with no further therapy when disease remains stable. Murphy et al. [17] provided methodology for estimating mean response to a dynamic regime under sequential randomization. Lunceford et al. [11] introduced estimators that account for second randomization and censoring for estimating the survival distribution and mean restricted survival time for treatment regimes in a two-stage randomized design. Murphy [15] constructed estimators of optimal dynamic treatment regimes using experimental or observational longitudinal data. Wahed and Tsiatis [23, 24] presented the most efficient estimator for the survival distributions utilizing additional information from auxiliary variables. Guo and Tsiatis [5] proposed a weighted risk set estimator (WRSE) on the basis of counting process and risk sets [4]. In addition, they also used time-varying measurement

for the indicator of response and consent. Lokhnygina and Helterbrand [10] implemented the inverse weighting [19] in the Cox regression methods for the two-stage randomization design. Furthermore, a consistent estimator for the log hazard in the Cox regression model and a pseudo-score statistic were also proposed to compare treatment regimes. Thall et al. [21] used a family of generalized logistic regression models and an approximate Bayesian method to evaluate multicourse treatment regimes. Murphy and Bingham [16] applied a new methodology to the identification of potential treatment components and screening out insignificant ones for developing dynamic treatment regimes.

Cox model provides an effective and efficient way of analyzing survival data in clinical trials. Lokhnygina and Helterbrand [10] extended the widely used Cox regression method to two-stage randomization designs. However, it applies only to the comparison of treatment regimes that share the same second stage therapy. This significantly limits its application in general settings. Furthermore, it does not take into account the fact that the intermediate response is a time-varying phenomenon. In this article, we propose a generalized Cox proportional hazards model that not only applies to comparisons of any combination of any number of treatment regimes, but also allows the intermediate response to appear as a time-varying-covariate. We also provide contrasts for comparing treatment regimes and describe corresponding hypothesis testing process.

This chapter is organized as follows. In Section 3.2, we introduce notation used in this article. In Section 3.3, we introduce the model framework for estimation and testing. In Section 3.4, a Monte Carlo simulation study is carried out to examine the performance of the estimates and the corresponding hypothesis tests. In Section 3.5, we fit the model to the high risk neuroblastoma dataset to compare overall survival for different neuroblastoma treatment regimes.

3.2 NOTATION

Consider a two-stage randomization design as depicted in Figure 1, where patients are randomized to J initial treatments, namely, A_1, A_2, ..., A_{J-1}, A_J. Patients who responded to

the initial treatment and provided consent to further participation are subsequently randomized to K maintenance treatments, B_1, B_2, ..., B_{K-1}, B_K. Denote by A_jB_k the treatment regime "treat with A_j followed by B_k if the patient responds and consents to subsequent maintenance therapy." Our goal is to compare regimes A_jB_k, $j = 1, ..., J$ and $k = 1, ..., K$ based on the overall survival. The set of observed data from this design can be described as

$$\{V_i, X_{ji}, R_i, R_iT_i^R, R_iZ_{ki}, U_i, \Delta_i\},$$

where V_i denotes the baseline covariates; X_{ji} is the indicator for jth initial treatment, $X_{ji} = 1$ if the ith patient was assigned to A_j as initial treatment, and $X_{ji} = 0$ if otherwise; R_i is the indicator for response and consent, $R_i = 1$ if the ith patient responded to the initial treatment and consent to further randomization, and $R_i = 0$ if otherwise; T_i^R indicates the time to response and consent; Z_{ki} is the indicator for kth maintenance treatment, $Z_{ki} = 1$ if the ith patient was assigned to B_k as maintenance treatment, and $Z_{ki} = 0$ if otherwise (note that Z_{ki} is defined only when $R_i = 1$); and U_i denotes the observed death ($\Delta_i = 1$) or censoring time ($\Delta_i = 0$). We assume independent right censoring which is customary in the application of Cox model. Also define $R_i(t) = 1$ if response and consent have been observed by time t for the ith patient, and $R_i(t) = 0$ if otherwise. Note that $R_i(t)$ can be expressed as $R_i(t) = R_iI(T_i^R < t)$ and indicates the time-varying response and consent status.

3.3 THE MODEL

Patients randomized according to a two-stage design (Figure 1) cannot be uniquely attached to a single regime, since patients not responding to an initial treatment could be considered following all regimes that share that initial treatment. For example, consider the hypothetical data from four patients presented in Table 7. Patient P1 is assigned to initial treatment A_1, responded to A_1, and then is assigned to maintenance treatment B_1, and hence is consistent with regime A_1B_1. Patient P2 is also assigned to initial treatment A_1 but did not respond to A_1, and thus is consistent with both regimes A_1B_1 and A_1B_2. Similarly, patient P3 is treated consistent to the regime A_2B_2, and patient P4 to both regimes A_2B_1 and A_2B_2. Thus

Table 7: Data from four hypothetical patients in a two-stage randomization design.

Patient	Initial treatment	Respond?	Maintenance treatment	Regime consistent with
P1	A_1	Yes	B_1	A_1B_1
P2	A_1	No		A_1B_1, A_1B_2
P3	A_2	Yes	B_2	A_2B_2
P4	A_2	No		A_2B_1, A_2B_2

standard survival analysis tools such as Kaplan-Meier, log-rank or Cox proportional hazards models are not directly appropriate. We therefore propose to use the following version of Cox model

$$\begin{aligned}\lambda(t) &= \lambda_0(t)\exp\left\{\sum_{j=1}^{J-1}\beta_j^{(1)}X_j + \beta^{(2)}R(t) + \sum_{j=1}^{J-1}\beta_j^{(3)}X_jR(t) + \sum_{k=1}^{K-1}\beta_k^{(4)}Z_kR(t)\right.\\ &\quad \left. + \sum_{j=1}^{J-1}\sum_{k=1}^{K-1}\beta_{jk}^{(5)}X_jZ_kR(t) + \gamma^TV\right\}\\ &\equiv \lambda_0(t)\exp\left\{G(t)\beta\right\}, \end{aligned} \tag{3.1}$$

where $\lambda(t)$ is the general hazard function at time t; $\lambda_0(t)$ denotes the baseline hazard function (when all the covariates equal to 0); $R(t)$ denotes the time-varying measurement of response and consent as defined before; β is the vector of coefficients denoted as $\beta = \left[\beta_1^{(1)},\ldots,\beta_{J-1}^{(1)},\beta^{(2)},\beta_1^{(3)},\ldots,\beta_{J-1}^{(3)},\beta_1^{(4)},\ldots,\beta_{K-1}^{(4)},\beta_{11}^{(5)},\ldots,\beta_{(J-1)(K-1)}^{(5)},\gamma\right]^T$; and $G(t)$ is the vector of all covariates stacked in the same order as β. Note that in the above model, $R(t)$ is used as a covariate, which by definition may be affected by the initial treatment and thus is not exogenous in nature. The goal of this model is neither to draw conclusion about $R(t)$, nor to draw inferences on the initial treatment. Instead this model aims to assess the effect of a treatment regime, which is a function of both $R(t)$ and the initial treatment. Therefore, we do not consider it necessary to elaborate on the endogenous nature of $R(t)$.

For $J = K = 2$ (i.e. only two treatment options available at each stage), the above model can be written as

$$\lambda(t) = \lambda_0(t)\exp\left\{\beta_1^{(1)}X_1 + \beta^{(2)}R(t) + \beta_1^{(3)}X_1R(t) + \beta_1^{(4)}Z_1R(t) + \beta_{11}^{(5)}X_1Z_1R(t) + \gamma^TV\right\} \tag{3.2}$$

Based on model (3.2), the hazard functions for four treatment regimes, namely, A_1B_1, A_1B_2, A_2B_1, and A_2B_2 could be written as

$$\lambda_{A_1B_1}(t) = \lambda_0(t)\exp\left\{\beta_1^{(1)} + (\beta^{(2)} + \beta_1^{(3)} + \beta_1^{(4)} + \beta_{11}^{(5)})R(t) + \gamma^T V\right\};$$

$$\lambda_{A_1B_2}(t) = \lambda_0(t)\exp\left\{\beta_1^{(1)} + (\beta^{(2)} + \beta_1^{(3)})R(t) + \gamma^T V\right\};$$

$$\lambda_{A_2B_1}(t) = \lambda_0(t)\exp\left\{(\beta^{(2)} + \beta_1^{(4)})R(t) + \gamma^T V\right\};$$

$$\lambda_{A_2B_2}(t) = \lambda_0(t)\exp\left\{\beta^{(2)}R(t) + \gamma^T V\right\}.$$

A similar model structure for linear regression was proposed in Murphy and Bingham (2009), however, the model did not include time-varying response structure. Under model (3.2), comparisons of treatment regimes in terms of their hazards can be interpreted by the coefficient vector $\beta = \left[\beta_1^{(1)}, \beta^{(2)}, \beta_1^{(3)}, \beta_1^{(4)}, \beta_{11}^{(5)}, \gamma\right]^T$. When comparing treatment regimes sharing the same initial therapy, e.g., comparing A_1B_1 to A_1B_2 and comparing A_2B_1 to A_2B_2, the null hypothesis $H_1 : \lambda_{A_1B_1}(t) = \lambda_{A_1B_2}(t)$ is equivalent to $H_1 : \beta_1^{(4)} + \beta_{11}^{(5)} = 0$, and the null hypothesis $H_2 : \lambda_{A_2B_1}(t) = \lambda_{A_2B_2}(t)$ is equivalent to $H_2 : \beta_1^{(4)} = 0$. When comparing treatment regimes sharing the same maintenance therapy, e.g., comparing A_1B_1 to A_2B_1 and comparing A_1B_2 to A_2B_2, the null hypothesis $H_3 : \lambda_{A_1B_1}(t) = \lambda_{A_2B_1}(t)$ is equivalent to $H_3 : \beta_1^{(1)} = 0; \beta_1^{(3)} + \beta_{11}^{(5)} = 0$, and the null hypothesis $H_4 : \lambda_{A_1B_2}(t) = \lambda_{A_2B_2}(t)$ is equivalent to $H_4 : \beta_1^{(1)} = \beta_1^{(3)} = 0$. Furthermore, for comparing all four treatment regimes in a simple two-stage randomization design, the null hypothesis $H_5 : \lambda_{A_1B_1}(t) = \lambda_{A_1B_2}(t) = \lambda_{A_2B_1}(t) = \lambda_{A_2B_2}(t)$ can be interpreted as $H_5 : \beta_1^{(1)} = \beta_1^{(3)} = \beta_1^{(4)} = \beta_{11}^{(5)} = 0$.

In all of the above cases, no single relative risk can be used to estimate the relative effect of one regime vs. the other, since a time-varying measurement of response and consent is involved in their hazard functions. For example, the hazard ratio at time t for the regime A_1B_1 and A_1B_2 is given by $\lambda_{A_1B_1}(t)/\lambda_{A_1B_2}(t) = \exp\left\{\left(\beta_1^{(4)} + \beta_{11}^{(5)}\right)R(t)\right\}$, which is not a constant. It depends on whether the patient responded by time t or not. Thus if two patients received the same initial therapy A_1 and did not respond by time t, then their hazards are identical, which is what one would expect. However, if these two patients had responded by

time t, then their hazard ratio would be $\exp\left(\beta_1^{(4)} + \beta_{11}^{(5)}\right)$. Model (3.1) can also be extended to compare any combination of any number of treatment regimes (see discussion).

Coefficients of Cox model with time-dependent covariates are usually estimated using maximum likelihood method through partial likelihood [2, 22]. The log partial likelihood function based on model (3.1) is given by

$$l(\beta) \;=\; \sum_{i=1}^{n} \int_0^{\infty} \left\{ Y_i(t) G_i(t)\beta - \log\left(\sum_p Y_p(t) \exp\left[G_p(t)\beta\right] \right) \right\} dN_i(t),$$

where $N_i(t) = I(U_i \leq t, \Delta_i = 1)$ and $Y_i(t) = I(U_i \geq t)$. The coefficients are obtained by solving the score equations defined below

$$U(\beta) = \sum_{i=1}^{n} \int_0^{\infty} \left\{ G_i(t) - \overline{g}(\beta, s) \right\} dN_i(s) = 0,$$

where

$$\overline{g}(\beta, s) = \frac{\sum Y_p(s) \exp\left[G_p(s)\beta\right] G_p(s)}{\sum Y_p(s) \exp\left[G_p(s)\beta\right]}.$$

It is well-known that the estimated coefficients $\hat{\beta}$ are asymptotically normally distributed with mean β and variance covariance matrix Σ, which is usually estimated by $\mathcal{I}^{-1}(\hat{\beta})$, where

$$\mathcal{I}^{-1}(\hat{\beta}) = \left\{ \sum_{i=1}^{n} \int_0^{\infty} \frac{\sum Y_p(s) \exp\left[G_p(s)\hat{\beta}\right] \left[G_p(s) - \overline{g}(\hat{\beta}, s)\right]' \left[G_p(s) - \overline{g}(\hat{\beta}, s)\right]}{\sum Y_p(s) \exp\left[G_p(s)\hat{\beta}\right]} dN_i(s) \right\}^{-1}.$$

For details, see Therneau and Grambsch [22] Section 3. The estimation is done using the Newton-Raphson algorithm in statistical packages such as SAS [20] and R [18]. Both the PHREG procedure in SAS and the *coxph* function in the "survival" package of R can easily fit this Cox proportional hazards model.

After fitting model (3.2), the coefficient estimates $\hat{\beta}$ and their estimated variance covariance matrix $\hat{\Sigma}$ are obtained. Then the null hypotheses described above can be tested using Wald chi-square tests. For example, the null hypothesis $H_3 : \lambda_{A_1B_1}(t) = \lambda_{A_2B_1}(t)$ could be tested using a Wald chi-square test statistic with two degrees of freedom. The test statistic can be written as

$$\chi_2^2 = (A\hat{\beta})^T (A^T \hat{\Sigma} A)^{-1} (A\hat{\beta}),$$

where

$$A = \begin{bmatrix} 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 1 \end{bmatrix}.$$

This test statistics then is compared to the critical values from a χ^2_2 distribution.

3.4 SIMULATION STUDY

The performance of the generalized Cox proportional hazards model was evaluated by conducting a Monte Carlo simulation study. For simplicity, and to maintain similarity with the neuroblastoma dataset, a simple two-stage randomization design allowing two treatment options at each stage was chosen. Overall sample size n was varied between 200 and 800 with step-wise increments of 200. Indicator for initial treatment A_1 (X_1) was sampled from Bernoulli(0.5) distribution. V was chosen to be a one-dimensional auxiliary covariate generated from normal distribution with mean 1 and standard deviation 0.5. We generated the "response time" T^R from Exponential(α). We followed Leemis et al. (1990) to generate survival time from Cox model with time-dependent covariates. Let u be a single observation drawn from a uniform distribution, Uniform(0,1), and λ be the exponential baseline function, namely, $\lambda_0(t) = \lambda$. Then the response status for the ith patient was defined by

$$R_i = \begin{cases} 0 & \text{if } 0 < -log(1-u_i)/\lambda < T_i^R \exp{(\beta_1^{(1)} X_{1i} + \gamma V_i)}, \\ 1 & \text{if } -log(1-u_i)/\lambda \geq T_i^R \exp{(\beta_1^{(1)} X_{1i} + \gamma V_i)}. \end{cases}$$

Indicator for maintenance treatment B_1 (Z_1) was sampled from Bernoulli(0.5) distribution, defined only under the condition that $R = 1$. Since our Cox proportional hazards model includes both time-change covariate and other fixed covariates, piecewise exponentially distributed death times were generated for nonresponders ($R = 0$) and responders ($R = 1$) [9]. The survival time for the ith patient was defined as

$$T_i = \begin{cases} \frac{-log(1-u_i)}{\lambda \exp{(\beta_1^{(1)} X_{1i} + \gamma V_i)}} & \text{if } R_i = 0, \\ \frac{-log(1-u_i) - T_i^R \lambda \exp{(\beta_1^{(1)} X_{1i} + \gamma V_i)}}{\lambda \exp{(\beta_1^{(1)} X_{1i} + \beta^{(2)} + \beta_1^{(3)} X_{1i} + \beta_1^{(4)} Z_{1i} + \beta_{11}^{(5)} X_{1i} Z_{1i} + \gamma V_i)}} + T_i^R & \text{if } R_i = 1. \end{cases}$$

Censoring time C was drawn from a Uniform$(0, \theta)$ distribution. These set-up ensured that survival time T follows a Cox proportional hazards model with time dependent measurement of response and consent $R(t)$ as defined in Section 3.2:

$$\lambda(t) = \lambda_0(t) \exp\left\{\beta_1^{(1)} X_1 + \beta^{(2)} R(t) + \beta_1^{(3)} X_1 R(t) + \beta_1^{(4)} Z_1 R(t) + \beta_{11}^{(5)} X_1 Z_1 R(t) + \gamma V\right\}.$$

Simulation parameters λ, α and θ were selected to achieve permutations of 40%, 50%, 60% response rate and 50%, 30% censoring percentage approximately, whereas other parameters $(\beta_1^{(1)}, \beta^{(2)}, \beta_1^{(3)}, \beta_1^{(4)}, \beta_{11}^{(5)}, \gamma)$ were chosen to reflect the status of different hypotheses in the true population. For simplicity, we planned to test only the following three null hypotheses: $H_1 : \lambda_{A_1B_1}(t) = \lambda_{A_1B_2}(t)$, $H_3 : \lambda_{A_1B_1}(t) = \lambda_{A_2B_1}(t)$, and $H_5 : \lambda_{A_1B_1}(t) = \lambda_{A_1B_2}(t) = \lambda_{A_2B_1}(t) = \lambda_{A_2B_2}(t)$. These hypotheses are equivalent to $H_1 : \beta_1^{(4)} + \beta_{11}^{(5)} = 0$, $H_3 : \beta_1^{(1)} = 0; \beta_1^{(3)} + \beta_{11}^{(5)} = 0$, and $H_5 : \beta_1^{(1)} = \beta_1^{(3)} = \beta_1^{(4)} = \beta_{11}^{(5)} = 0$ respectively. Therefore, in the first simulation scenario, the set of coefficients $\{\beta_1^{(1)}, \beta^{(2)}, \beta_1^{(3)}, \beta_1^{(4)}, \beta_{11}^{(5)}, \gamma\}$ was chosen to be $\{-0.5, -0.8, 0.5, 1, -1, -0.5\}$ to study the performance of Wald chi-square tests for $H_1 : \lambda_{A_1B_1}(t) = \lambda_{A_1B_2}(t)$ (note that $\beta_1^{(4)} + \beta_{11}^{(5)} = 0$, which indicates that in the true population H_1 is true); in the second scenario, the set of coefficients was chosen to be $\{0, 0.1, -0.8, 2, 0.8, -0.5\}$ to study the performance of Wald chi-square tests for $H_3 : \lambda_{A_1B_1}(t) = \lambda_{A_2B_1}(t)$ (note that $\beta_1^{(1)} = 0; \beta_1^{(3)} + \beta_{11}^{(5)} = 0$); in the third scenario, the set of coefficients was chosen to be $\{0, 0.8, 0, 0, 0, -0.5\}$ to study the performance of Wald chi-square tests for $H_5 : \lambda_{A_1B_1}(t) = \lambda_{A_1B_2}(t) = \lambda_{A_2B_1}(t) = \lambda_{A_2B_2}(t)$ (note that $\beta_1^{(1)} = \beta_1^{(3)} = \beta_1^{(4)} = \beta_{11}^{(5)} = 0$). For each scenario, 2,000 samples of size n were drawn and model (3.2) described in Section 3.3 was fitted to each sample using *coxph* function in R.

Simulation results are shown in Tables 8-11. Table 8 shows the estimated coefficients, standard errors (SE), Monte-Carlo standard errors (MCSE) and coverage probabilities (CP) of 95% confidence intervals under scenario I. The estimated coefficients were approximately unbiased. The largest absolute bias (0.05) occurred for $\beta^{(2)}$ under a smaller sample size of 400, a relatively larger censoring percentage of 50% and a smaller response rate of 40%. In most cases absolute biases were less than 0.03. The standard errors were close to the Monte-Carlo standard errors, demonstrating that the estimated standard errors were consistent.

The coverage probabilities of 95% confindence intervals were within the range of 93.9% to 96.1%, attaining the nominal level of 95% in most of the cases. The results were similar for both 40% and 60% response rates. However, as expected, both absolute biases and standard errors became smaller with increasing sample size and decreasing censoring percentage. In Tables 9 and 10, we presented the simulation results under scenarios II and III respectively. Similar to the results of scenario I, under scenario II, estimators performed well, with small absolute biases. Coverage probabilities were in the interval of 94.2% and 96.3%. We observed even better performance under scenario III, with absolute biases even smaller (less than 0.02). The coverage probabilities under scenario III were between 94.2% and 95.9%.

Table 8: Simulation results under scenario I. True values of coefficients are $\beta_1^{(1)} = -0.5, \beta^{(2)} = -0.8, \beta_1^{(3)} = 0.5, \beta_1^{(4)} = 1.0, \beta_{11}^{(5)} = -1.0, \gamma = -0.5$. Est = mean of estimated coefficients, Bias = | Estimate - True |, SE = mean of estimated standard errors, MCSE = Monte-Carlo standard deviation of the estimators and CP = coverage probability of 95% CI.

		$n = 400$									
Response		50% censoring					30% censoring				
Rate	Coef	Est	Bias	SE	MCSE	CP(%)	Est	Bias	SE	MCSE	CP(%)
40%	$\beta_1^{(1)}$	-0.51	0.01	0.182	0.184	95.3	-0.51	0.01	0.153	0.154	95.2
	$\beta^{(2)}$	-0.85	0.05	0.333	0.335	96.1	-0.83	0.03	0.266	0.271	94.8
	$\beta_1^{(3)}$	0.53	0.03	0.445	0.456	94.7	0.52	0.02	0.343	0.360	93.9
	$\beta_1^{(4)}$	1.04	0.04	0.366	0.372	95.2	1.03	0.03	0.298	0.300	94.9
	$\beta_{11}^{(5)}$	-1.04	0.04	0.537	0.544	95.5	-1.03	0.03	0.416	0.418	95.3
	γ	-0.51	0.01	0.149	0.152	95.0	-0.51	0.01	0.124	0.127	94.4
60%	β_1	-0.51	0.01	0.249	0.258	94.9	-0.51	0.01	0.188	0.191	95.0
	$\beta^{(2)}$	-0.82	0.02	0.299	0.303	95.0	-0.82	0.02	0.244	0.250	94.5
	$\beta_1^{(3)}$	0.52	0.02	0.391	0.401	95.2	0.51	0.01	0.309	0.317	94.5
	$\beta_1^{(4)}$	1.02	0.02	0.270	0.271	95.7	1.02	0.02	0.237	0.238	95.3
	$\beta_{11}^{(5)}$	-1.02	0.02	0.399	0.401	95.0	-1.03	0.03	0.335	0.338	95.5
	γ	-0.51	0.01	0.153	0.155	94.9	-0.51	0.01	0.126	0.128	94.8
		$n = 600$									
Response		50% censoring					30% censoring				
Rate	Coef	Est	Bias	SE	MCSE	CP(%)	Est	Bias	SE	MCSE	CP(%)
40%	$\beta_1^{(1)}$	-0.50	0.00	0.148	0.147	94.9	-0.50	0.00	0.125	0.124	95.1
	$\beta^{(2)}$	-0.81	0.01	0.267	0.266	95.5	-0.80	0.00	0.214	0.212	95.5
	$\beta_1^{(3)}$	0.50	0.00	0.357	0.364	94.7	0.49	0.01	0.277	0.280	95.4
	$\beta_1^{(4)}$	1.01	0.01	0.293	0.296	95.6	1.00	0.00	0.240	0.238	95.7
	$\beta_{11}^{(5)}$	-1.01	0.01	0.430	0.432	95.3	-1.00	0.00	0.336	0.339	95.2
	γ	-0.50	0.01	0.121	0.121	94.8	-0.51	0.01	0.101	0.103	94.5
60%	$\beta_1^{(1)}$	-0.50	0.00	0.202	0.199	95.6	-0.50	0.00	0.153	0.151	95.1
	$\beta^{(2)}$	-0.81	0.01	0.242	0.242	95.0	-0.80	0.00	0.198	0.198	94.8
	$\beta_1^{(3)}$	0.50	0.00	0.315	0.314	95.2	0.50	0.00	0.251	0.246	95.6
	$\beta_1^{(4)}$	1.01	0.01	0.218	0.221	95.3	1.00	0.00	0.192	0.196	94.7
	$\beta_{11}^{(5)}$	-1.01	0.01	0.322	0.325	95.4	-1.01	0.01	0.272	0.272	95.3
	γ	-0.51	0.01	0.124	0.125	94.8	-0.51	0.01	0.102	0.104	94.4

Table 9: Simulation results under scenario II. True values of coefficients are $\beta_1^{(1)} = 0, \beta^{(2)} = 0.1, \beta_1^{(3)} = -0.8, \beta_1^{(4)} = 2.0, \beta_{11}^{(5)} = 0.8, \gamma = -0.5$. Est = mean of estimated coefficients, Bias = | Estimate - True |, SE = mean of estimated standard errors, MCSE = Monte-Carlo standard deviation of the estimators and CP = coverage probability of 95% CI.

$n = 400$											
Response		50% censoring					30% censoring				
Rate	Coef	Est	Bias	SE	MCSE	CP(%)	Est	Bias	SE	MCSE	CP(%)
40%	$\beta_1^{(1)}$	-0.00	0.00	0.199	0.204	94.5	-0.00	0.00	0.158	0.159	95.0
	$\beta^{(2)}$	0.07	0.03	0.316	0.316	96.2	0.08	0.02	0.240	0.245	94.7
	$\beta_1^{(3)}$	-0.83	0.03	0.512	0.523	95.5	-0.82	0.02	0.360	0.370	94.5
	$\beta_1^{(4)}$	2.04	0.04	0.327	0.333	95.9	2.03	0.03	0.266	0.266	95.5
	$\beta_{11}^{(5)}$	0.83	0.03	0.533	0.541	95.4	0.82	0.02	0.399	0.387	96.3
	γ	-0.50	0.00	0.148	0.151	94.8	-0.50	0.00	0.123	0.125	94.8
60%	$\beta_1^{(1)}$	-0.01	0.01	0.259	0.267	95.1	-0.00	0.00	0.208	0.211	95.1
	$\beta^{(2)}$	0.07	0.03	0.316	0.327	94.8	0.09	0.01	0.242	0.248	94.6
	$\beta_1^{(3)}$	-0.82	0.02	0.490	0.514	95.0	-0.81	0.01	0.343	0.341	95.7
	$\beta_1^{(4)}$	2.04	0.04	0.284	0.288	95.4	2.03	0.03	0.225	0.232	94.6
	$\beta_{11}^{(5)}$	0.83	0.03	0.462	0.476	95.1	0.80	0.00	0.331	0.327	95.0
	γ	-0.50	0.00	0.150	0.150	95.0	-0.50	0.00	0.125	0.127	94.5
$n = 600$											
Response		50% censoring					30% censoring				
Rate	Coef	Est	Bias	SE	MCSE	CP(%)	Est	Bias	SE	MCSE	CP(%)
40%	$\beta_1^{(1)}$	0.00	0.00	0.162	0.162	94.8	0.00	0.00	0.129	0.129	94.9
	$\beta^{(2)}$	0.09	0.01	0.254	0.256	95.4	0.10	0.00	0.195	0.192	95.4
	$\beta_1^{(3)}$	-0.83	0.03	0.409	0.415	95.4	-0.82	0.02	0.290	0.299	94.2
	$\beta_1^{(4)}$	2.02	0.02	0.263	0.262	95.3	2.01	0.01	0.215	0.213	95.6
	$\beta_{11}^{(5)}$	0.84	0.04	0.425	0.432	94.7	0.82	0.02	0.322	0.325	95.3
	γ	-0.51	0.01	0.120	0.122	94.8	-0.50	0.00	0.100	0.102	95.0
60%	$\beta_1^{(1)}$	0.00	0.00	0.211	0.212	94.7	0.00	0.00	0.169	0.166	95.5
	$\beta^{(2)}$	0.10	0.00	0.255	0.255	95.5	0.10	0.00	0.197	0.196	95.6
	$\beta_1^{(3)}$	-0.83	0.03	0.392	0.400	95.1	-0.81	0.01	0.278	0.283	94.8
	$\beta_1^{(4)}$	2.01	0.01	0.228	0.233	94.7	2.01	0.01	0.182	0.184	94.9
	$\beta_{11}^{(5)}$	0.83	0.03	0.369	0.375	95.1	0.81	0.01	0.268	0.269	95.2
	γ	-0.51	0.01	0.121	0.124	94.6	-0.51	0.01	0.101	0.103	95.0

Table 10: Simulation results under scenario III. True values of coefficients are $\beta_1^{(1)} = 0, \beta^{(2)} = 0.8, \beta_1^{(3)} = 0, \beta_1^{(4)} = 0, \beta_{11}^{(5)} = 0, \gamma = -0.5$. Est = mean of estimated coefficients, Bias = | Estimate - True |, SE = mean of estimated standard errors, MCSE = Monte-Carlo standard deviation of the estimators and CP = coverage probability of 95% CI.

		$n = 400$									
Response		50% censoring					30% censoring				
Rate	Coef	Est	Bias	SE	MCSE	CP(%)	Est	Bias	SE	MCSE	CP(%)
40%	$\beta_1^{(1)}$	-0.01	0.01	0.199	0.203	94.3	-0.01	0.01	0.162	0.163	95.3
	$\beta^{(2)}$	0.79	0.01	0.265	0.267	95.1	0.79	0.01	0.219	0.224	94.3
	$\beta_1^{(3)}$	0.02	0.02	0.362	0.368	94.4	0.01	0.01	0.300	0.310	94.2
	$\beta_1^{(4)}$	0.01	0.01	0.303	0.304	95.6	0.00	0.00	0.253	0.253	95.3
	$\beta_{11}^{(5)}$	-0.02	0.02	0.429	0.432	95.1	-0.01	0.01	0.357	0.355	95.5
	γ	-0.51	0.01	0.148	0.149	95.3	-0.51	0.01	0.123	0.126	94.4
60%	$\beta_1^{(1)}$	-0.01	0.01	0.254	0.262	95.1	-0.00	0.00	0.204	0.206	95.0
	$\beta^{(2)}$	0.79	0.01	0.270	0.281	94.7	0.80	0.00	0.218	0.224	94.8
	$\beta_1^{(3)}$	0.02	0.02	0.361	0.376	94.2	0.01	0.01	0.291	0.298	94.5
	$\beta_1^{(4)}$	0.01	0.01	0.256	0.259	94.5	0.00	0.00	0.207	0.209	94.7
	$\beta_{11}^{(5)}$	-0.01	0.01	0.363	0.365	95.2	-0.01	0.01	0.293	0.292	95.9
	γ	-0.51	0.01	0.149	0.151	95.1	-0.50	0.00	0.122	0.126	94.2
		$n = 600$									
Response		50% censoring					30% censoring				
Rate	Coef	Est	Bias	SE	MCSE	CP(%)	Est	Bias	SE	MCSE	CP(%)
40%	$\beta_1^{(1)}$	0.00	0.00	0.161	0.162	94.7	0.00	0.00	0.132	0.131	95.7
	$\beta^{(2)}$	0.81	0.01	0.214	0.214	95.3	0.80	0.00	0.178	0.176	95.8
	$\beta_1^{(3)}$	-0.01	0.01	0.293	0.296	95.6	0.00	0.00	0.244	0.247	94.9
	$\beta_1^{(4)}$	-0.01	0.01	0.244	0.244	95.6	-0.00	0.00	0.205	0.205	95.2
	$\beta_{11}^{(5)}$	0.01	0.01	0.346	0.347	95.2	0.00	0.00	0.289	0.292	94.8
	γ	-0.51	0.01	0.120	0.120	94.8	-0.51	0.01	0.100	0.102	94.9
60%	$\beta_1^{(1)}$	0.00	0.00	0.206	0.207	95.2	0.00	0.00	0.166	0.163	95.4
	$\beta^{(2)}$	0.81	0.01	0.219	0.217	95.8	0.81	0.01	0.177	0.177	95.7
	$\beta_1^{(3)}$	-0.01	0.01	0.293	0.296	94.8	-0.01	0.01	0.236	0.237	94.9
	$\beta_1^{(4)}$	-0.00	0.00	0.207	0.208	95.6	-0.00	0.00	0.168	0.172	95.0
	$\beta_{11}^{(5)}$	-0.00	0.00	0.293	0.296	94.8	0.00	0.00	0.238	0.242	94.7
	γ	-0.51	0.01	0.121	0.123	94.4	-0.51	0.01	0.099	0.102	95.0

Table 11 gives the Type I errors or powers of Wald chi-square tests under different scenarios for samples of sizes 400 and 600. Scenario I was generated based on the null hypothesis $H_1 : \lambda_{A_1B_1}(t) = \lambda_{A_1B_2}(t)$, so one would expect that the rejection rates for null hypothesis H_1 would be close to the nominal level of 0.05. The simulation results show rejection rates for testing H_1 to be near 0.05. The powers for the two other null hypotheses H_3 and H_5 under scenario I were maintained above 0.96, with a small increase resulting from an increase in the sample size. Scenario II was generated based on the null hypothesis $H_3 : \lambda_{A_1B_1}(t) = \lambda_{A_2B_1}(t)$. Similar to the rejection rates for null hypothesis H_1, type I error was well-maintained (~ 0.05) for this scenario, and the powers for the null hypotheses H_1 and H_5 were all equal to 1.00. Scenario III was generated based on the null hypothesis $H_5 : \lambda_{A_1B_1}(t) = \lambda_{A_1B_2}(t) = \lambda_{A_2B_1}(t) = \lambda_{A_2B_2}(t)$. Because null hypothesis H_5 implies null hypotheses H_1 and H_3, the rejection rates for all three null hypotheses under scenario III were close to 0.05. These results imply that comparative hypothesis testing can be performed maintaining adequate type I errors from the proposed model.

3.5 ANALYSIS OF NEUROBLASTOMA DATASET

In the neuroblastoma study, all patients were treated with induction chemotherapy first. Then 379 eligible patients without progressive disease participated in the first stage randomization, with 190 patients assigned to chemotherapy and 189 patients assigned to a combination of myeloablative chemotherapy, total-body irradiation, and transplantation of autologous bone marrow purged of cancer cells (ABMT). A total of 176 patients either had progressive disease or declined further randomization, so only 203 patients participated in the second stage randomization, with 102 patients assigned to cis-RA and 101 patients assigned to no further therapy. Thus, there are four possible treatment regimes in the neuroblastoma study: (i) treat with chemotherapy followed by cis-RA if no progressive disease (CCR); (ii) treat with chemotherapy followed by no cis-RA if no progressive disease (CNR); (iii) treat with ABMT followed by cis-RA if no progressive disease (ACR); (iv) treat with ABMT followed by no cis-RA if no progressive disease (ANR).

Table 11: Wald chi-square test results under scenarios I, II and III based on samples of sizes 400 and 600. $H_1 : \lambda_{A_1B_1}(t) = \lambda_{A_1B_2}(t)$, $H_3 : \lambda_{A_1B_1}(t) = \lambda_{A_2B_1}(t)$, and $H_5 : \lambda_{A_1B_1}(t) = \lambda_{A_1B_2}(t) = \lambda_{A_2B_1}(t) = \lambda_{A_2B_2}(t)$

		$n = 400$					
		50% censoring			30% censoring		
		Type I error/Power			Type I error/Power		
Scenario	Response Rate	H_1	H_3	H_5	H_1	H_3	H_5
I	40%	0.049	0.968	0.968	0.047	0.996	0.996
	50%	0.050	0.972	0.989	0.054	0.998	0.999
	60%	0.052	0.987	0.994	0.057	0.999	0.999
II	40%	1.000	0.049	1.000	1.000	0.049	1.000
	50%	1.000	0.059	1.000	1.000	0.052	1.000
	60%	1.000	0.058	1.000	1.000	0.049	1.000
III	40%	0.055	0.046	0.045	0.052	0.052	0.055
	50%	0.053	0.054	0.055	0.048	0.050	0.048
	60%	0.051	0.055	0.055	0.046	0.048	0.055
		$n = 600$					
		50% censoring			30% censoring		
		Type I error/Power			Type I error/Power		
Scenario	Response Rate	H_1	H_3	H_5	H_1	H_3	H_5
I	40%	0.051	0.998	1.000	0.059	1.000	1.000
	50%	0.041	1.000	1.000	0.051	1.000	1.000
	60%	0.050	1.000	1.000	0.052	1.000	1.000
II	40%	1.000	0.053	1.000	1.000	0.047	1.000
	50%	1.000	0.050	1.000	1.000	0.045	1.000
	60%	1.000	0.047	1.000	1.000	0.048	1.000
III	40%	0.055	0.051	0.051	0.053	0.052	0.053
	50%	0.054	0.044	0.049	0.052	0.054	0.052
	60%	0.055	0.046	0.048	0.048	0.048	0.043

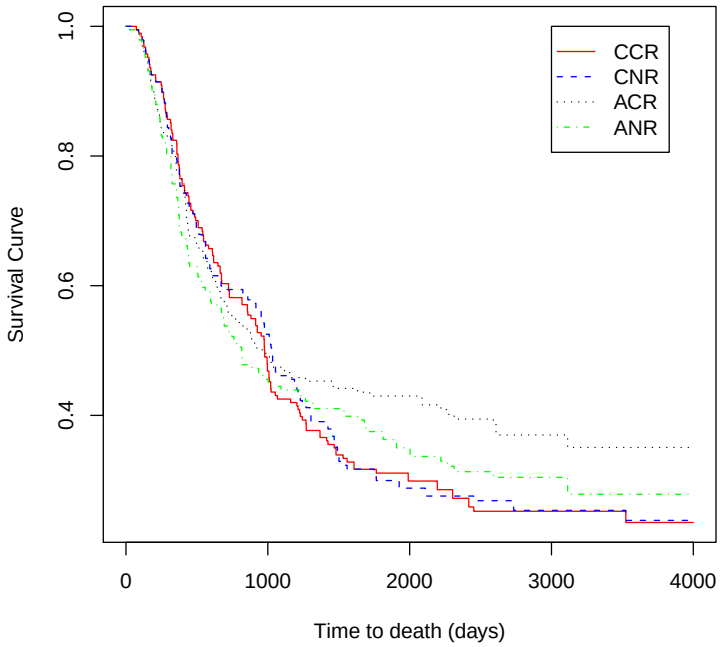

Figure 4: Overall survival curves under four treatment regimes in the neuroblastoma study. CCR: "treat with chemotherapy followed by cis-RA if no progressive disease", CNR: "treat with chemotherapy followed by no cis-RA if no progressive disease", ACR: "treat with ABMT followed by cis-RA if no progressive disease", ANR: "treat with ABMT followed by no cis-RA if no progressive disease"

Table 12: Wald chi-square test results for the neuroblastoma dataset. CCR: "treat with chemotherapy followed by cis-RA if no progressive disease", CNR: "treat with chemotherapy followed by no cis-RA if no progressive disease", ACR: "treat with ABMT followed by cis-RA if no progressive disease", ANR: "treat with ABMT followed by no cis-RA if no progressive disease"

	df	Test Statistic	P-value
$H_1 : \lambda_{CCR}(t) = \lambda_{CNR}(t)$	1	0.06	0.81
$H_2 : \lambda_{ACR}(t) = \lambda_{ANR}(t)$	1	2.20	0.14
$H_3 : \lambda_{CCR}(t) = \lambda_{ACR}(t)$	2	3.92	0.14
$H_4 : \lambda_{CNR}(t) = \lambda_{ANR}(t)$	2	0.47	0.79
$H_5 : \lambda_{CCR}(t) = \lambda_{CNR}(t) = \lambda_{ACR}(t) = \lambda_{ANR}(t)$	4	5.45	0.24

We first used the weighted risk set estimator (WRSE) [5] to estimate the overall survival curves. Overall survival curves under these four treatment regimes are presented in Figure 4. Apparently survival curves are close to each other during the first three years. They somewhat deviate from each other at later times but do not meet the criteria for statistical significance in adjusted analysis described as follows. We fitted the Cox proportional hazards model (3.2) to this data, including auxiliary covariates age, Evans stage, MYCN oncogene amplification (MYCN), histology, ferritin and initial response to induction chemotherapy. These covariates were identified as the potential prognostic factors diagnosed in Matthay et al. [12]. The covariate Evans stage was grouped as "stage 4," "stages other than stage 4" and "unknown." Histology was grouped as "favorable," "unfavorable" and "unknown." Ferritin was grouped as "normal," "elevated" and "unknown." Initial response to induction chemotherapy contained 8 levels: CR(complete response), VGPR(very good partial response), PR(partial response), SD(stable disease), MR(mixed response), PD(progressive disease), NR(no response) and missing. We categorized it into "CR/VGPR," "PR," "SD/MR," "PD" and "unknown" as was done by clinicians, see Matthay et al. [12].

Several different hypotheses comparing the treatment regimes were tested. The results

are summarized in Table 12. To test if there was a significant difference in the hazards of treatment regimes sharing the same initial treatment "chemotherapy," we set up the hypothesis $H_1 : \lambda_{CCR}(t) = \lambda_{CNR}(t)$. The p-value from the Wald test was equal to 0.81, implying that there was no statistically significant difference in the hazards of treatment regimes sharing the same initial treatment "chemotherapy." In other words, for patients who were assigned to initial treatment "chemotherapy," there was no difference in the overall survival whether they continued with maintenance treatment "cis-RA" or "no further therapy." The hypothesis that there was no significant difference in the hazards of treatment regimes sharing the same initial treatment "ABMT" was then tested using $H_2 : \lambda_{ACR}(t) = \lambda_{ANR}(t)$. The p-value for this test was 0.14, which would mean that for patients who were assigned to "ABMT" as initial treatment, there was no difference in the overall survival whether they continued with maintenance treatment "cis-RA" or "no further therapy." The hypotheses tests for difference in the hazards of treatment regimes sharing the same maintenance treatment "cis-RA" or "no further therapy," namely, $H_3 : \lambda_{CCR}(t) = \lambda_{ACR}(t)$ and $H_4 : \lambda_{CNR}(t) = \lambda_{ANR}(t)$, resulted in p-values 0.14 and 0.79 respectively, demonstrating that for patients who were assigned to "cis-RA" as maintenance treatment, regardless of which initial therapy they were assigned to, there was no difference in their overall survival, and the same was true for patients who were assigned to "no further therapy" as maintenance treatment. Subsequently, the difference in the hazards of four treatment regimes was examined through $H_5 : \lambda_{CCR}(t) = \lambda_{CNR}(t) = \lambda_{ACR}(t) = \lambda_{ANR}(t)$. The hazards of four treatment regimes were not statistically significantly different with p-value being 0.24. Thus, there was no difference in the overall survival irrespective of which initial treatment patients were assigned to and which maintenance treatment they were subsequently assigned to.

4.0 CONCLUSIONS

In Chapter 2, we demonstrated the use of the Nelson-Aalen estimator, proportional hazards model and accelerated failure time model for estimating the effects of treatment regimes from two-stage randomization designs. We also demonstrated how to compare different regimes in terms of their hazards using the Fleming-Harrington two-sample tests.

The simulation study showed that survival estimates could differ when a model other than the true model was fitted. Thus, the survival estimates were affected somewhat by the choice of distributions when fitting the accelerated failure time model. The proportional hazards model provided slightly biased estimates at earlier time points, however, the survival estimates obtained using the NA estimator were unbiased. The performance of the Nelson-Aalen estimator, proportional hazards model and accelerated failure time model were also evaluated at other response rates, censoring percentages, and for various sample sizes. We observed similar results using the proportional hazards model and accelerated failure time model at different censoring percentages, however, the Nelson-Aalen estimator provided biased estimates in small samples. When the response rate is as small as 40% and the overall sample size is relatively small such as 400, all the three methods show some bias in the survival estimates due to the small sample size in each subgroup.

Furthermore, the simulation study also showed that the rejection rates obtained using all the methods were similar to each other under all scenarios, demonstrating that the Fleming-Harrington two-sample test was robust regardless of the methods for estimating the survival quantities. When we utilized Fleming-Harrington two-sample tests to compare different treatment regimes in terms of their hazards, six pairs of null hypotheses were tested separately. In this circumstance, how small a p-value is considered significant needs further discussion. As we know, many statistical techniques have been developed for protecting

the Type I errors in multiple comparisons, e.g. Bonferroni correction, Holm's sequential rejection procedure, etc. Similar techniques could possibly be adopted here. However, we decided to pursue this in a separate research study. The methodology proposed here resembles the pattern-mixture models in the missing data literature ([14] Chapter 16), where the parameter estimates are estimated for each missing data pattern and then overall estimate is calculated as a weighted average of the pattern-specific estimates. If we look closely at equations (2.6)-(2.9), we see that for each strategy, the survival function is calculated as the weighted average of the two sequence(pattern)-specific survival estimates.

In Chapter 3, we proposed a generalized Cox proportional hazards model for comparing dynamic treatment regimes from sequentially randomized designs. In the simulation study we examined the performance of the proposed model fitting and showed that it performed well for moderate to large samples of sizes 200 to 800. Even in a large percentage of 50% censoring, the estimates were approximately unbiased and the coverage probabilites were consistent with the nominal level. The model was used to analyze the neuroblastoma dataset. Our analysis showed that neuroblastoma treatment regimes were similar in terms of overall survival, even though the survival probability at specific time points may be significantly different in analysis separated by stages [12].

The methodology proposed can be used to analyze survival data from sequentially assigned treatment trials or studies, regardless of the number of stages of treatment or number of available treatment options at each stage. Although two-stage randomization designs were used for demonstration throughout the article, the model also applies to multistage randomization designs with more than two stages. For example, under a three-stage randomization

design, the Cox model can be written as

$$\begin{aligned}\lambda(t) &= \lambda_0(t)\exp\Bigg\{\sum_{j=1}^{J-1}\beta_j^{(1)}X_j + \beta^{(2)}R_1(t) + \sum_{j=1}^{J-1}\beta_j^{(3)}X_jR_1(t) + \sum_{k=1}^{K-1}\beta_k^{(4)}Z_kR_1(t) \\ &+ \sum_{j=1}^{J-1}\sum_{k=1}^{K-1}\beta_{jk}^{(5)}X_jZ_kR_1(t) + \beta^{(6)}R_2(t) + \sum_{j=1}^{J-1}\beta_j^{(7)}X_jR_2(t) + \sum_{k=1}^{K-1}\beta_k^{(8)}Z_kR_2(t) \\ &+ \sum_{j=1}^{J-1}\sum_{k=1}^{K-1}\beta_{jk}^{(9)}X_jZ_kR_2(t) + \sum_{p=1}^{P-1}\beta_p^{(10)}Y_pR_2(t) + \sum_{j=1}^{J-1}\sum_{p=1}^{P-1}\beta_{jp}^{(11)}X_jY_pR_2(t) \\ &+ \sum_{k=1}^{K-1}\sum_{p=1}^{P-1}\beta_{kp}^{(12)}Z_kY_pR_2(t) + \sum_{j=1}^{J-1}\sum_{k=1}^{K-1}\sum_{p=1}^{P-1}\beta_{jkp}^{(13)}X_jZ_kY_pR_2(t) + \gamma^TV\Bigg\},\end{aligned}$$

where $R_1(t)$ indicates the time-varying response and consent status after first stage treatment; $R_2(t)$ denotes the time-varying measurement of response and consent after second stage treatment; and Y_p is the indicator for pth treatment at third stage. As the number of stages involved in a design increases, it becomes increasingly complex to explicitly write down the Cox model, as the number of parameters increases rapidly. However, the implementation using standard software packages is straightforward.

The inclusion of $R(t)$ as a covariate in the model demands further discussion. At first glance, one may hesitate to use $R(t)$ (an endogenous covariate) in the model with the fear of blurring the direct effect of the initial treatment with its indirect effect through response. But the goal of such analysis is to assess the regime effect, which by definition puts the direct and indirect effects in one bin. The inclusion of $R(t)$ in the model should merely be seen as a tool to facilitate the comparisons of different treatment regimes.

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