FRAILTY MODELING OF SEMI-COMPETING RISKS DATA

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A THESIS SUBMITTED

FOR THE DEGREE OF MASTER OF SCIENCE

DEPARTMENT OF EPIDEMIOLOGY AND PUBLIC HEALTH

NATIONAL UNIVERSITY OF SINGAPORE

2010

ACKNOWLEDGEMENTS

I will like to extend most heartfelt thanks to a number of people.

To my supervisor A/Prof Tai Bee Choo, co-supervisor Dr Xu Jinfeng, and advisor Prof Jack Kalbfleisch, who have been ever so generous with their encouragement and statistical support. Thank you for your valuable inputs from the initial concept of the study to statistical advice and comments on the writing of the thesis. And also, for forking out the time amidst your busy schedules to attend the many meetings which we have had for discussion and troubleshooting. Also, thank you for giving me the opportunity to attend the ISCB conference in 2008. It has been an invaluable experience.

To Elizabeth and Zhaojin, for being such wonderful classmates. Thank you for your help when I was debugging my programming code and clarifying my understanding of theoretical concepts.

To Dr Joseph Wee, for providing the nasopharyngeal cancer dataset for further analyses in this project.

To Hwee Bee, for providing background information on the nasopharyngeal cancer dataset.

To Prof Yudi Pawitan, Prof Marie Reilly and Chuen Seng, for your comments on the proposed method. Your input has certainly helped to better my understanding of the proposed model and to improve the initial model formulation. Also, thanks so much for the pointers when I was preparing for the oral presentation for ISCB.

To my colleagues and friends Xueling, Sharon, Yang Qian, Shu Mei, Suo Chen, Peiling, Brenda, Ching Ni, Cuiling, Feng Ping, Huijiao, Safiyya, Ai-Leen, Hui Qi, Zhen Ning and many others for your friendship and motivation.

Last but not the least, to my family, especially my sister Gek Shan, for all your love and support.

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Summary

In biomedical research involving time-to-event data, individuals may be susceptible to several possible outcomes. When an individual experiences more than one event in the follow-up process, this gives rise to multiple failure time data. In the modeling of such data, a random effect or 'frailty' term is often introduced to accommodate the dependence between event times. In this paper, we consider a semi-competing risks framework, where a subject may experience two distinct types of events - terminal or non-terminal. In particular, the terminal event censors the non-terminal event but not vice versa. We propose frailty modeling for such data, where the frailty corresponds to an unknown subject-specific quantity which affects both events, leading to a dependence in their times of occurrence. Given frailty, a three-path compartment model is used to describe such data. We investigated the dependence structure between the events, as well as the covariate effects on each event. Extensive simulation studies were conducted to assess the performance of the proposed method. We also applied our methodology to data from a randomized clinical trial of nasopharyngeal cancer, where a positive dependence between recurrence and death was observed, indicating that relapse quickens the occurrence of death. This indicates that the association between non-terminal and terminal events needs to be taken into account, so as to achieve more accurate estimates, as shown in our study.

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Chapter 1: Introduction

1.1 Competing risks

Time-to-event data, which is usually encountered in prospective studies, are often handled using some form of survival analytical methods. In such studies, an individual provides follow-up information on the time-to-event of interest and the censoring indicator denoting whether or not the event has occurred.[1] However in clinical trials comparing therapeutic interventions involving multiple survival outcomes, a subject may experience several distinct types of failures. This type of data is commonly referred to as competing risks. A competing risk can be defined as an occurrence which may preclude the onset of the event of interest, or may modify the probability of the onset of the event of interest.[2] A special case of competing risks occurs if only the first of all possible outcomes is observed, with all other outcomes being competing events.

Competing risks data can arise under various circumstances with different research objectives. One possible research aim will be to analyze how different events can occur in a disease process, without any specific interest in a particular outcome. For example, investigators may be interested in examining different responses that can occur in patients with respect to changing drug dosage in a treatment process, such as in a study looking at how cerebral blood flow changes with different dosages of inhaled xenon gas in xenon CT scanning.[3] Alternatively,

investigators may be interested in the occurrence of a specific event, with all other types of events being regarded as interferences or competing events in the process leading to the event of interest. As an example, investigators may be interested in comparing the incidence of distant metastasis between chemo-radiotherapy and radiotherapy in a nasopharyngeal clinical trial.[4] While some subjects may have experienced distant metastasis, others have experienced competing events such as local recurrence or intercurrent death as a first event. Further examples of endpoints encountered in competing risks data are found in Pintilie.[5]

Table 1: Examples of endpoints together with their possible competing risks[5]

Event of interest	Possible competing risks
Local relapse	Relapse at other sites or death without local relapse
Distant relapse	Relapse at other sites or death without distant relapse
Cause-specific survival	Death due to other causes
Non-fatal myocardial infarction (MI)	Cardiovascular death non-vascular death, non-fatal stroke and angina

In the analyses of clinical trials involving time-to-event outcomes, disease-free and overall survival distributions are often presented to provide an insight of treatment efficacy.[5] While overall survival gives an indication of how long a patient survives from randomization till death, disease-free survival gives an idea of how long a patient survives without any disease symptom till a relapse or death. It is no doubt that relapse is the only event we can influence by treatment[6], and that it is also biologically plausible that the time to relapse is strongly correlated

with the time to death (i.e. the occurrence of relapse quickens the death process). Hence, it is of interest to investigate how treatment affects the chance of relapse, bearing in mind that an assessment of the effect of a particular intervention on relapse should not be isolated from its effect on progression to mortality, since censoring from mortality may be informative.

1.2 Semi-competing risks

If all types of failures are allowed to be observed until possibly censored for each subject, multivariate failure time data arises. However, an analysis of multivariate failure time data involving possible recurrent events may be complicated by dependent censoring from terminal events such as mortality or informative dropout. Events occurring due to this data structure are sometimes referred to as semi-competing risks, where a terminal event can censor a non-terminal outcome, but not vice versa.[7] In contrast to the approach adopted in the popular competing risks methodology where only the first event is of interest, semi-competing risks considers all possible occurrences of events in a natural disease process. For example, if death (a terminal event) occurs earlier, it will preclude the occurrence of relapse (a non-terminal event). However if relapse occurs earlier, both relapse and death may be observed.

Where multiple events are observed, it may be of interest to estimate and compare treatment efficacy for every outcome, with emphasis on the intermediate event. The importance of understanding how therapeutic interventions can bring about the occurrence of an intermediate event is underscored by Fine.[7] In the context of allogenic bone marrow transplants in leukemia patients, "the distribution of time without relapse corresponds to a setting where death from graft versus host disease is preventable".[7] In such instances, patients can either die following a relapse or following graft versus host disease (GVHD). Hence, it will be interesting to understand how bone marrow transplants affect the risk of relapse, GVHD, and death after the occurrence of these intermediate events. It will also be valuable to know the extent to which relapse hastens the occurrence of death.

Currently, literature on semi-competing risks data is limited; and competing risks methods are often used to analyze semi-competing risks data. Hence in order to appropriately account for the semi-competing risks data framework, analytical methods for estimating and modeling such data are proposed and discussed in section 1.6.

1.3 Frailty

Most survival models assume that the risk of the study population for certain outcomes is homogeneous. However, the homogeneity assumption may not be valid as it is not possible to measure all covariates related to the disease of interest because of constraints in resources. The presence of unmeasured disease-related covariates may result in a heterogeneous sample. Frailty accounts for the unexplained heterogeneity, which arises mainly due to related individuals or events, by introducing random effects into the survival models.[8] Examples of data describing related individuals are the Minnesota Twin Family Study which attempts to assess the impact of genetic and environmental effects on the development of psychological traits, Danish Twin Study, and the Twins and Multiple Births Association heritability study (TAMBAhs) in Birmingham.

To elaborate on the meaning of frailty, consider multivariate survival data with possible correlation between clustered event times. In the context of survival times of related individuals, related individuals constitute a "cluster". Where multiple events are observed for the same individual, the individual constitutes a "cluster". Frailty models formulate the dependence of clustered event times by introducing a cluster-specific random effect, which is multiplicative on the baseline hazard function, to account for heterogeneity within the same cluster.

1.4 Objectives and Outline of thesis

1.4.1 Objectives

Semi-competing risks data arises when both non-terminal and terminal events occur and are of analytical importance. In survival data, a non-terminal event and a terminal event usually refer to morbidity and mortality respectively. These two events are usually correlated; and censoring of morbidity by mortality is informative. Hence, in this thesis, we want to get a more precise estimate of the effect size (in particular, treatment effect) for each clinical outcome, and also to characterize the correlation between morbidity and mortality.

We consider strategies for analyzing covariate effects by using frailty models to describe the dependence structure and to assess treatment efficacy with respect to the terminal and non-terminal events. The compartment model is further described in Chapter 3. It is similar to an illness-death model[9], which describes the risk of moving from one disease-state to another. While the illness-death model may be bi-directional (that is, a patient can progress from the state of recovery after treatment to disease recurrence and vice versa), the compartment model is uni-directional (that is, the change in state is from recovery to disease recurrence only).

1.4.2 Outline

We have given a description of competing risks in the previous sections. Sections 1.1 and 1.2 describe the type of data giving rise to the analytical framework of competing and semi-competing risks respectively. Where multiple events of an individual can be observed and only the first event is considered, this analytical framework constitutes a special case and the most common form of competing risks data. If all data points are involved in the analysis, then other analytical procedures are required. Section 1.3 briefly defines what is meant by "frailty". Section 1.4 presents the aims and outline of this thesis. Section 1.5 illustrates terminologies and analytical procedures associated with competing risks. Section 1.6 summarizes the development of methodologies proposed specifically for analyzing semi-competing risks data. Section 1.7 discusses why current competing risks methodologies may not be suitable for semi-competing risks data. In addition, it addresses the limitations of semi-competing risks methods proposed thus far, and describes how our proposed method can resolve some of these limitations.

Chapter 2 illustrates the use of existing methods for semi-competing risks data with some clinical examples. Chapter 3 gives an overview of the proposed compartment model. The formulation of each path in the compartment model is explicitly characterized in this chapter, together with the algorithm used to derive the parameter estimates. In the same chapter, we also suggest a graphical method for checking the adequacy of the model. In Chapter 4, simulation studies are

conducted to evaluate the performance of the proposed model. Treatment effects, association between terminal and non-terminal outcomes, censoring proportions and sample sizes are varied to investigate their impact on the model. Results relating to the precision of the parameter estimates are presented and discussed. Chapter 5 applies the proposed method to a nasopharyngeal cancer clinical trial (NPC) dataset. We quantify the dependence between relapse and death, as well as compare the treatment effects (chemo-radiotherapy versus radiotherapy) on relapse and death respectively. In addition, adequacy of the overall model fit to the NPC data is checked. Finally, Chapter 6 summarizes and provides some discussion on the compartment model approach for analyzing semi-competing risks data. Further scope for future work extending our proposed method, is also discussed in this chapter.

1.5 Methods for competing risks data

The Kaplan-Meier[10] (KM) estimator is commonly used to report disease-free and overall survival distributions. However, when competing risks exist, this approach may not be an appropriate measure for estimating the survival distribution of the primary event. An example involves distant recurrence as the primary event and local-regional recurrences as the competing type of failure. The Kaplan-Meier approach assumes that censoring is non-informative, that is, the censoring mechanism is independent of the event of interest.[2] Hence, the

application of the KM method for estimating event-specific probability of competing risks can lead to a bias in the estimate.[11]

Referring to the nasopharyngeal clinical trial described in Section 1.1, it was observed that distant relapse was the most frequent site of first relapse (38 out of 48 first relapses were distant in R and 18 out of 27 in CRT).[4] Thus, it was of interest to examine the incidence of distant metastasis. However, other competing events, such as loco-regional recurrence or death, may preclude the observation of distant metastasis. Therefore, the assumption of non-informative censoring under the naive KM approach may not be appropriate in this study since it is anticipated that the occurrence of loco-regional recurrence may have an effect on distant metastasis, and vice versa. For instance, the occurrence of loco-regional recurrence may indicate a more rapid development of distant metastasis, should the course of treatment remain status quo. This change in risk for distant metastasis, after an occurrence of loco-regional recurrence, indicates a dependency between loco-regional recurrence and distant metastasis. Furthermore, if death occurs first, it will inherently prevent any future observation of distant metastasis. However, the KM method censors competing events and treats the occurrence of the competing events (death and loco-regional recurrence) as though they do not alter (or add information to) the probability of observing distant metastasis.

In view of the limitations of KM for analyzing competing risks data, appropriate tools were developed. In general, there are 2 approaches for analyzing

competing risks data. They are namely, the bivariate random variable and multiple decrement model methods, which are described in greater detail below.

Bivariate random variable

In this approach, time-to-event data is represented by the pair (T, C) for each individual, where $T \geq 0$ is the observation time of the first event and C indicates the type of event which occurs at time $T = t$. C takes on a value of 0 if the observation is censored administratively, and i ($i = 1, 2, \ldots, p$) if the first event that occurs is of type i.

In the presence of competing risks, the corresponding cause-specific hazard (CSH, $h_i(t)$), which describes the instantaneous rate of occurrence of the i^{th} event at time t given covariate X, is written as

$$h_i(t) = \lim_{\delta t \to 0} \{ \frac{\Pr(t < T \leq t + \delta t, C = i \mid T > t, X)}{\delta t} \}$$

The cumulative incidence function (also called sub-distribution) is used to describe the probability that the i^{th} event occurs before or at time t (CIF_i), given X. It is expressed as

$$CIF_i(t \mid X) = \Pr(T \leq t, C = i \mid X)$$

CSH is different from the hazard of the sub-distribution (also called sub-hazard) introduced by Gray (1988)[12]. For the i^{th} event, the sub-hazard is defined as

$$\varphi_i(t \mid X) = \lim_{\delta t \to 0}\{\frac{\Pr(t < T \le t + \delta t, C = i \mid (T > t) \cup (T \le t \cap C \ne i), X)}{\delta t}\}$$

$$= \frac{f_i(t \mid X)}{S_i(t \mid X)}$$

Where $f_i(t|X)$ and $S_i(t|X)$ are the sub-density and survival functions of the sub-distribution respectively.

This construction of the hazard function may sound "unnatural", since it takes individuals who have failed from causes other than cause *i* before time *t* into its computation. However, in reality, individuals who have failed from cause $j \neq i$ may not be at risk of cause *i* at time *t*. Hence, this could lead to a difficulty in interpreting an individual's risk of failure from cause *i* at time *t* if he has died from other causes at time *t* - 1.

While Gray's sub-hazard is introduced mainly to allow for testing and modeling of covariate effects, other tests for equality for cumulative incidence have been proposed by Pepe and Mori[13] and Lunn[5].

Multiple decrement model

In this approach, a multivariate survival model is used to analyze competing risks data, where each individual is assumed to have a potential time to event. An observation time $T = \min\left(\bar{T}_1, \bar{T}_2, \ldots, \bar{T}_p\right)$ is defined, supposing that there are potentially *p* causes of failure and $\bar{T}_i$ is the time to the i^{th} event where *i* =

1, 2, …, *p*. When the first event is observed, the times to the other remaining events are considered to be latent.

Given covariate effects *X*, a joint survival function (also known as the multiple decrement function) can be written as $S(\bar{T}_1, \bar{T}_2, ..., \bar{T}_p; X) = \Pr(\bar{T}_1 > t_1, \bar{T}_2 > t_2, ..., \bar{T}_p > t_p; X)$. As it is still not clear how time-dependent effects may be incorporated in this multivariate model, covariate effects are assumed to be time-invariant.

Correspondingly, the sub-hazard for the i^{th} event $\varphi_i(t)$ and cause-specific hazard $h_i(t)$ in the multiple decrement model framework is

$$\varphi_i(t) = \lim_{\delta t \to 0} \{ \frac{\Pr(t < T \le t + \delta t, C = i \mid T > t; X)}{\delta t} \}$$
$$= - \frac{\partial \log(S(t_1, t_2, ..., t_p; X))}{\partial t_i} \Bigg|_{t_1 = t_2 = ... = t_p = t}$$

and

$$h_i(t) = - \frac{\partial \log(S_i(t; X))}{\partial t} .$$

It is noted that functions of $S(\bar{T}_1, \bar{T}_2, ..., \bar{T}_p; X)$, which cannot be expressed in terms of the cause-specific hazards, are generally non-identifiable. One example is the marginal function of the latent failure time, which cannot be estimated from the data without making any assumption. The marginals can only be estimated by

assuming that event times are independent, so that the cause-specific hazard will be equal to the hazard of the marginal function for each event type.

Choice of method for competing risks data

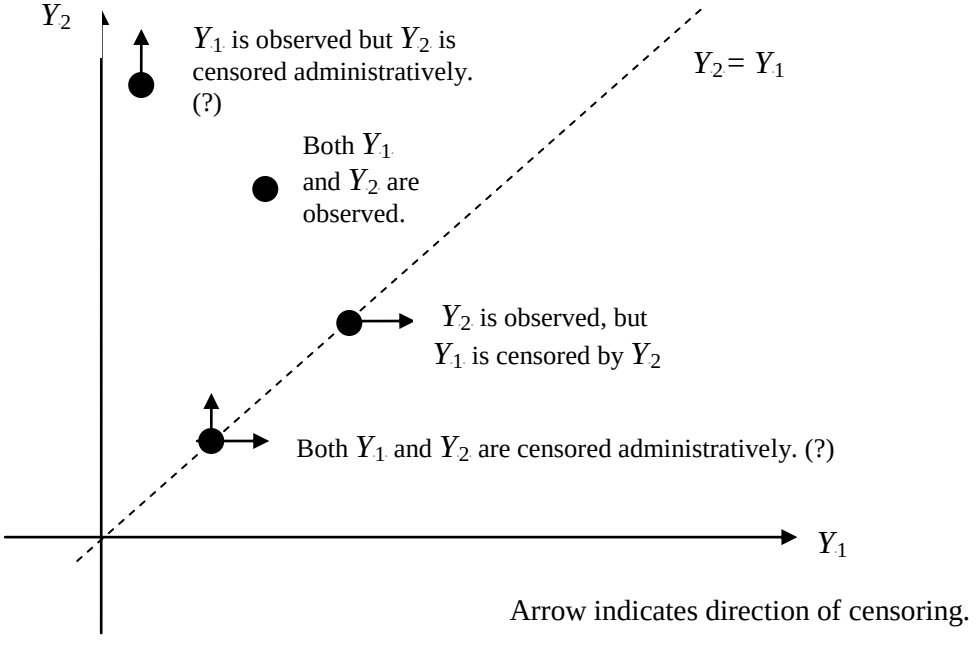
The choice of analytical method depends on the research question. If the objective of a study is to test if a covariate has any impact on the biological mechanism, it is suggested that the multiple decrement model be used. Results drawn from this model apply to a virtual world where competing risks are absent. In contrast, the bivariate random variable approach will probably be preferred if it is of interest to compare observed probabilities of events directly while accounting for competing risks.[17]

1.6 Current methods proposed for semi-competing risks data

There is currently limited literature for semi-competing risks data[7,18,19]. In order to evaluate the dependence structure between non-terminal and terminal event times, Fine *et al.* formulated the Clayton or gamma frailty copula model in the upper wedge where Y_1 (time to non-terminal event) $\leq Y_2$ (time to terminal event)[7]. A copula is a function which associates a bivariate distribution function $H(y_1, y_2)$ to its one-dimensional marginal distribution functions $F(y_1)$ and $G(y_2)$ defined by the relationship $H(y_1, y_2) = C(F(y_1), G(y_2))$[20]. This means that

a copula is a multivariate distribution function defined on the space $[0, 1]^p$ such that each of its p marginal distribution follows a uniform distribution on [0, 1]. Fine *et al*[7,18] utilizes the marginal distribution of the non-terminal event under weaker, but similar assumptions, to those used in multiple decrement models for competing risks. Within the observable region of $Y_1 \leq Y_2$, the joint survival function of the two times is expressed as $\{S_{Y_1}(y_1)^{1-\theta} + S_{Y_2}(y_2)^{1-\theta} - 1\}^{\frac{1}{1-\theta}}$ where $\theta \geq 1$ and $0 \leq Y_1 \leq Y_2 \leq \infty$. $S_{Y_1}(y_1)$ and $S_{Y_2}(y_2)$ are marginal survival functions for the times to the non-terminal and terminal events respectively.

Figure 1: Diagram illustrating structure of semi-competing risks data[25]



Since the joint survival function originates from the gamma frailty model, there are nice properties associated with it. For example, the association parameter in the Clayton's copula can also be interpreted as the predictive hazard ratio which measures the relative risk of death to relapse, apart from measuring the degree of dependence between the times to terminal and non-terminal events. In addition, it is associated with the conditional Kendall's tau, which is yet another measure of correlation.[21] The appropriateness of the Clayton model on the upper wedge is important since inferences pertaining to the marginal survival function of the non-terminal event time rely on the model specification in the observable region. Hence, checking of model adequacy is performed through an extension of Oakes' estimators.[22,23] A goodness-of-fit statistic can be obtained from the distance between two estimators from $U(\theta)$ with different weights $W(.)$, where

$$U(\theta) = \sum_{q<v} W(\tilde{S}_{qv}, \tilde{R}_{qv}) B_{qv} \{\Delta_{qv} - \frac{\theta}{1+\theta}\} \quad \text{for both } q \text{ and } v = 1, \ldots, N \text{ subjects}.$$

For q and $v = 1, \ldots, N$ subjects, the parameters in $U(\theta)$ are described as follows:

$$\tilde{S}_{qv} = \min(\tilde{Y}_{1,qv}, \tilde{Y}_{2,qv}, \tilde{C}_{qv}), \ \tilde{R}_{qv} = \min(\tilde{Y}_{2,qv}, \tilde{C}_{ij}),$$

$$\tilde{B}_{qv} = I(\tilde{Y}_{1,qv} < \tilde{Y}_{2,qv} < \tilde{C}_{qv}), \ \Delta_{qv} = I\{(Y_{1,q} - Y_{1,v})(Y_{2,q} - Y_{2,v}) > 0\},$$

$$\tilde{Y}_{1,qv} = \min(Y_{1,q}, Y_{1,v}) \text{ and } \tilde{Y}_{2,qv} = \min(Y_{2,q}, Y_{2,v})$$ [24]

Fine *et al*[7] has shown that the estimates are robust to the misspecification of the copula. The Clayton model may provide a reasonably good approximation to other popular classes of distributions, such as the bivariate exponential, bivariate log-normal and Gumbel copula[25]

It was not known how covariates influence the relationship between a non-terminal and terminal outcome in Fine et al[7]. Thus, Ghosh[19] considered the testing of constant dependence across strata of a discrete covariate, by evaluating whether the dependence between the non-terminal and terminal event is the same for both treatment and placebo groups. Hypothesis testing of constant dependence on the upper wedge is facilitated through the cross-ratio function defined as

$$\theta(y_2, y_1) = \frac{\lambda_{Y_1}(y_2 \mid Y_2 = y_1)}{\lambda_{Y_1}(y_2 \mid Y_2 \geq y_1)}$$

where $\lambda_{Y_1}(y_1 \mid H) = \lim_{\Delta y_1 \to 0} \frac{d}{dy_1} \Pr(Y_1 < y_1 + \Delta y_1 \mid Y_1 \geq y_1, Y_2 \in H)$ and $H \in (0, \infty)$. Y_1 and Y_2 are the times to the non-terminal and terminal events respectively.

Hence, the null hypothesis that the dependence between the two event times is constant across levels of a discrete covariate can be written as:

$$H_0: \theta_d = \theta,$$

where $\theta_d = \theta(y_2, y_1 \mid D = d) = \frac{\lambda_{Y_1}(y_2 \mid Y_2 = y_1, D = d)}{\lambda_{Y_1}(y_2 \mid Y_2 \geq y_1, D = d)}$ and d corresponds to the level of the covariate.

Testing the above hypothesis is also the same as testing for interaction between the covariate X and the association parameter θ in the observable region of the event times. However, it is noted that the above test is only valid if the Clayton gamma frailty copula model was true. Therefore, the appropriateness of using the Clayton copula for the data analyzed should be assessed before checking for constant dependence[19].

While the degree of dependence between event times has been analyzed via the non-parametric concordance statistic, Dignam *et al*[26] exemplified dependence between event times by using parametric models based on complete pairs of Y_1 and Y_2 event times. The marginal distributions are estimated by treating censored/ unobservable Y_1's as missing data. EM algorithm was used to estimate the parameters governing the forms of the survival function of Y_1 and of the survival function of Y_2 conditional on Y_1. However, the form of the dependence structure between Y_1 and Y_2 was not explicitly characterized in their paper.

Although the Clayton copula has generally been used for semi-competing risks data, it may not be suitable for certain data structures. However, modifications can be made to it depending on the type of data. This is shown in Jiang[27] where the Clayton's copula model was modified into a conditional one for left-truncated and right-censored registry data. Instead of the usual $\{S_{Y_1}(y_1)^{1-\theta} + S_{Y_2}(y_2)^{1-\theta} - 1\}^{\frac{1}{1-\theta}}$ where $\theta \geq 1$ and $0 \leq Y_1 \leq Y_2 \leq \infty$ as postulated above, the model was modified as $\{R_a(y_1)^{1-\theta} + S_a(y_2)^{1-\theta} - 1\}^{\frac{1}{1-\theta}}$ where $S_a(y_2)$ is the conditional survival function given that Y_2 is greater than a, and $R_a(y_1)$ is the survival function conditional on Y_1 greater than a and dependent censoring by Y_2. The Lynden-Bell estimator was constructed to estimate marginal survival function for the non-terminal and terminal events under mild assumptions. It is a product-limit estimator derived from non-parametric maximum likelihood arguments for truncated data $Y_{1,n}$, which is observable only if $Y_{1,n} \geq Y_{2,n}$ for $n = 1, 2, \ldots, N$ subjects. It is denoted as

$1-\hat{F}(t)=\prod_{s\le t}(1-\frac{\Delta L_N(s)}{R_N(s)})$, where $L_N(s)=\sum_{n=1}^{N} I(Y_{2,n}Y_{1,n}\le s)$ and $R_N(s)=\sum_{n=1}^{N} I(Y_{2,n}\le s\le Y_{1,n})$ [28,29]. However, it was noted that the Lynden-Bell estimator may not be appropriate for the survival function for the non-terminal event, as the estimator may not be monotone or well-defined. This phenomenon occurs especially in its tail of the survival distribution where heavy censoring by the terminal event usually occurs. Therefore, restriction of the estimation interval was put in place to circumvent the problem. To reiterate, the conclusions inferred will be valid if (1) the copula model describing the joint survival functions of the non-terminal and terminal event times was correctly specified, and (2) the survival function for the non-terminal event defined on the upper wedge where $Y_1 \le Y_2$ corresponds to the marginal of Y_1 defined on the lower wedge $Y_1 \ge Y_2$, where no data can be observed.

The conventional Clayton copula model could also be extended into a time-dependent copula, characterizing the correlation between events, to capture the informative censoring of Y_2 on Y_1. Knowledge of the impact of covariate effects on event times could be evaluated through a regression model. Non-linear estimating equations were used to solve for the parameter estimates. In addition, model checking through a graphical technique similar to the idea of a Q-Q plot was proposed[18].

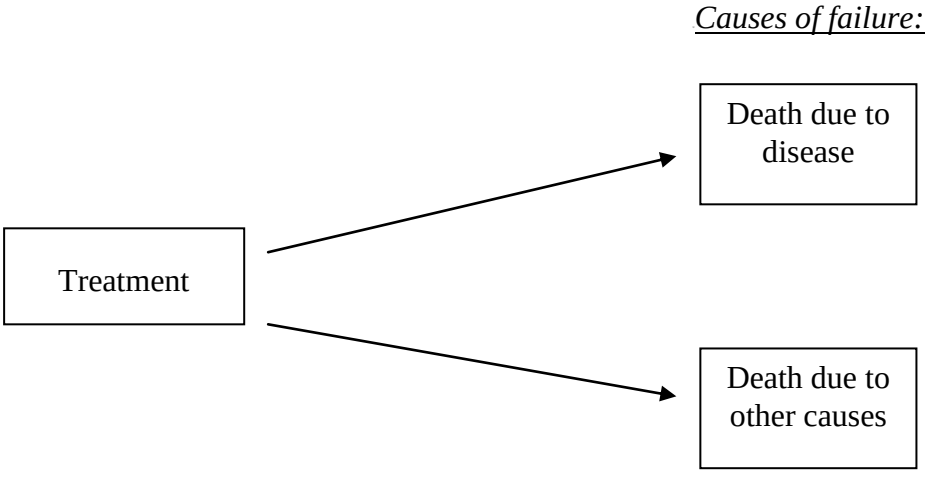
So far, all estimations made for the marginal distribution of the non-terminal event time were formulated based on the framework of the Clayton gamma frailty copula. Besides looking at the estimation of the survival function of the non-terminal event, other authors have looked at areas which included generalizing the semi-competing approach to include other copulas and to make inferences in terms of hypothesis testing. For instance, Lakhal *et al* generalized Fine's approach by illustrating that the semi-competing risks idea could be applied to all Archimedean copulas through simulations and applying them to study the correlation between times to relapse and death in patients with bone marrow transplants[21]. An Archimedean copula is a function C which maps $[0, 1]^2$ to $[0, 1]$ given by $C(u, v) = \psi^{[-1]}(\psi(u)+ \psi(v))$, where ψ is called the generator of C. ψ is a continuous monotonic decreasing convex function which maps $[0, 1]$ to $[0, \infty]$ such that $\psi(1) = 0$ and $\psi(0) = \infty$. $\psi^{[-1]}$ is the pseudo-inverse of ψ, which means that $\psi^{[-1]}(y) = \psi^{-1}(y)$ where y is an element in $[0, \psi(0)]$ and $\psi^{[-1]}(y) = 0$ for $y \geq \psi(0)$.[20] Most of the Archimedean copulas, which include the Clayton, Gumbel and Frank copulas, have closed-form solutions for its estimators. Apart from Lakhal[21], Hsieh and Wang[30] have also implemented Archimedean copulas in the analyses of semi-competing risks data. However, in their paper, they have suggested the use of separate Archimedean copula models for each covariate group while maintaining a monotonically increasing hazard function for the disease progression time under dependent censoring. Model checking and selection via bootstrap methods are also proposed.[30] Subsequently, Xu *et al*[31] argued that the notion of latent failure times is entertained in previous approaches since they usually construct mathematical models in both the observable and unobservable regions of the data. Hence, they

proposed a model constructed within the observable region of the data to accommodate covariates. In addition, frailty was used to account for the correlated endpoints (morbidity and mortality). Non-parametric maximum likelihood methods were used to estimate the parameters.

Thus far, methods concerning semi-competing risks data have been discussed in the context of the copula function. It is also possible to consider solving for parameter estimates in relation to this type of data via a multi-state modeling approach as in Siannis *et al*[32]. Using this approach, a continuous time model with Weibull time-varying hazards, assuming that transition rates depend only on the last state visited but not on the complete history of transitions, was adopted. The time for each subject used in the analysis was measured from the time since entry into the study to the starting time in the current state. It will be less appropriate to consider the analysis time as the time taken to travel in between any 2 states, i.e. having to reset to zero the time axis after the subject enters into a state, since the hazards vary with time. In addition, it was noted that estimates of the transition rates starting from censored events to a terminal event would be correlated and no unique solution of the likelihood would exist, without further model assumptions, in general.

1.7 Limitations of existing methods for semi-competing risks data

Competing risks methods have often been used for analyzing semi-competing risks data. The first-event methodology adopted in competing risks analysis is based on the premise that upon removal of one of the failures, the risks of failure on the remaining causes remain unchanged. That is, the development of the event of interest is independent of the progression of competing risks. In particular, the classical competing risk framework in which a subject may only fail from one of several distinct causes will probably be more applicable in a situation with several absorbing states. One such example, which considers death due to disease as the event of interest and death due to other causes as the competing risk event, is illustrated below.



While the first-event methodology will be appropriate for competing risks, it may not be the most suitable method for a data structure involving endpoints which follow a natural occurrence of events. Specifically in such naturally ordered

data involving a terminal event (death) and non-terminal event (recurrence), death has the ability to preclude the occurrence of recurrence but not the other way round. Then, censoring from mortality becomes informative. Furthermore, in this instance, it may be of interest to know the dependence structure between recurrence and death (and hence, to understand the predictive value of recurrence for death). The use of the first-event approach limits our ability to do so since subsequent events after the first would not form part of the data analyzed.

In order to utilize all subsequent events that occurred after the first so as to describe the data sufficiently, methods based on the weak assumption of marginals, which accounts for the dependence structure between all the occurrences of endpoints, have been proposed. They have been described in Section 1.6. In general, authors working on semi-competing risks methodology have considered variations within the basic model structure. These variations include the different types of copulas used to characterize the dependence between the non-terminal and terminal events, as well as the different types of survival models which can be used to describe the mathematical functions of the non-terminal and terminal events. Approaches, which could be used to incorporate covariates and to perform hypothesis testing, were also proposed.

However, as pointed out by Xu *et al*[31], these methods implied a kind of model formulation using latent times. Hence, the authors have proposed mathematical models which are constructed within the observable region of the event times. The models also allowed for varying hazards and treatment effects

depending on whether the non-terminal event has occurred prior to the terminal event. It is a generalization of the previous models put forward by other authors who have assumed that the effect of the occurrence of a non-terminal event on the terminal event has been fully explained by the correlation between the two events. The correlation is characterized by the copula model incorporated into the basic model formulation.

In this thesis, the idea conceptualized by Xu *et al*[31] is extended. Based on the original compartment model framework proposed, data is modeled within the observable region, that is, no marginal distribution for the non-terminal event is assumed. In the previous article, baseline hazards were regarded as a "nuisance" parameter in the solution of covariate effects such as treatment. However, it may be of interest to know the form of baseline hazards apart from the covariate effects. Therefore, we attempt to characterize the baseline hazards via parametric modeling in this thesis. In addition, goodness-of-fit assessments of the models, which have not been recommended by Xu *et al*[31], are proposed. The methodology is described in detail in Chapter 3.

1.8 Contribution to medical research

The work arising from this paper has been presented at the 29th Annual Conference of the International Society for Clinical Biostatistics (Copenhagen, Denmark); as well as at a seminar in the Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, both in 2008.

Chapter 2: Analysis of semi-competing risks data in the medical literature

While the Kaplan-Meier and Cox proportional hazards model are popular methods used to analyze survival data without competing events, the bivariate random variable method involving implementation of the cumulative incidence function is often used in analyses of competing risks data. However, these tools may not be reasonable for semi-competing risks data, which are widely encountered in the medical field. To our knowledge, no clinical paper has implemented the existing methods as described in Section 1.6. Current approaches used for analyzing semi-competing risks data are described in the following examples.

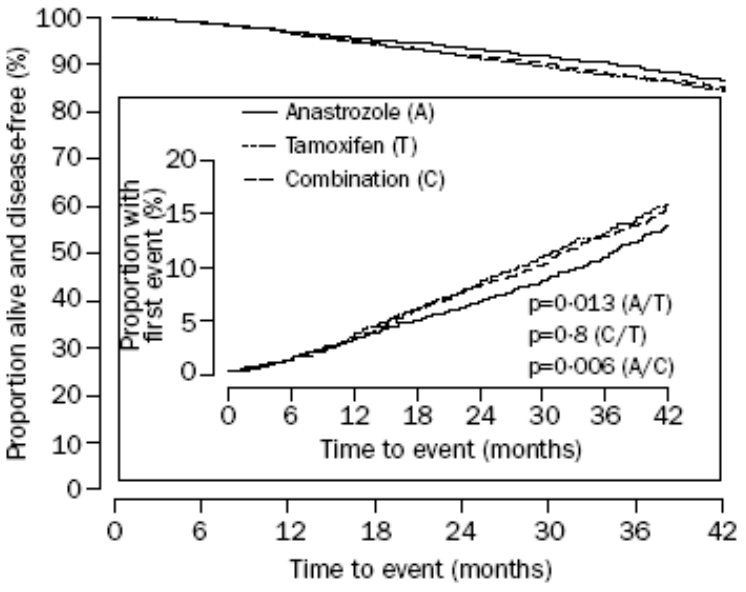
2.1 ATAC (Arimidex, Tamoxifen, Alone or in Combination) clinical trial

The ATAC (Arimidex, Tamoxifen, Alone or in Combination) randomized clinical trial involved 9366 postmenopausal women with localized breast cancer enrolled from 381 centers in 21 countries between 12 July 1996 and 24 March 2000. The primary aim of the trial was to ascertain the efficacy of anastrozole (alone, or in combination with tamoxifen) as compared with tamoxifen alone. The primary endpoint was disease-free survival (DFS), which was defined as the time

to the earliest occurrence of local or distant recurrence, new primary breast cancer, or death due to any cause. Secondary endpoints were time to a recurrence which includes new contralateral tumors but not patients who died from non-breast cancer causes before recurrence; and time to an incidence of new contralateral primary breast tumor.[33]

In this ATAC trial, both the log-rank test and Cox proportional hazards model were used to analyze disease-free survival (DFS) and outcomes under investigation based on an intention-to-treat approach. It was shown that as compared with women treated with only tamoxifen, DFS was significantly higher for patients on anastrozole (Hazard ratio, HR: 0.83; 95% CI: 0.71 - 0.96; $p = 0.013$) or a combination of anastrozole and tamoxifen (HR: 0.81; 95% CI: 0.70 - 0.94; $p = 0.006$). Figure 2 shows the Kaplan-Meier curves for DFS in the intention-to-treat population.

Figure 2: Kaplan-Meier curves depicting disease-free survival (i.e., all first events) for each treatment arm in the intention-to-treat population in the ATAC trial[33]



There did not seem to be a substantial difference in the number of patients who died (regardless of any cause of death) before a breast cancer recurrence (Table 2). When these patients were censored upon death, the hazards for the time to recurrence (including new tumors) in the anastrozole group was lower than the tamoxifen group (HR: 0.79; 95% CI: 0.67 - 0.94; p = 0.008). The benefit appeared to be comparable between the combination and tamoxifen groups (Figure 3).

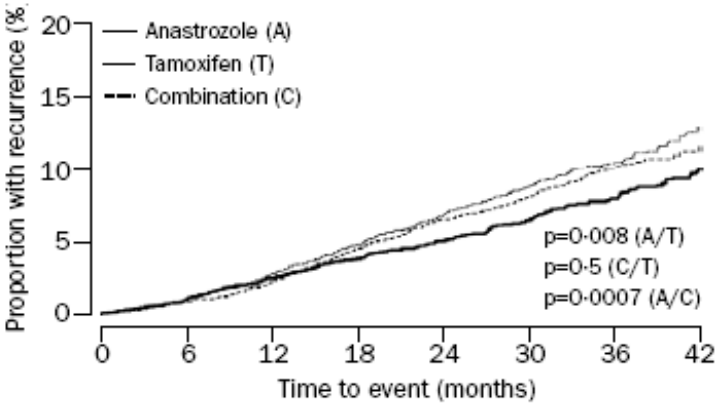
Table 2: Distribution of events stratified by the 3 treatment groups in the ATAC trial[33]

	Anastrozole (*n*=3125)	**Tamoxifen (*n*=3116)**	**Combination (*n*=3125)**	**Total (*n*=9366)**
First events				
Local recurrence	67	83	81	231
Distant recurrence[†]	158	182	204	544
Contralateral breast cancer	14	33	28	75
Invasive	9	30	23	62
Ductal carcinoma in-situ	5	3	5	13

Deaths before recurrence	78	81	70	229
Total	317	379	383	1079
Events at any time				
Distant recurrence[†]	180	203	232	615
Deaths after recurrence	122	122	145	389
All deaths	200	203	215	618

†: Includes 5 deaths (2 on anastrozole, 1 on tamoxifen, and 2 on the combination), which were attributed to breast cancer without prior information about recurrence.

Figure 3: Probability of recurrence in the intention-to-treat population in the ATAC trial[33]



From Table 2, it was also noted that there was a substantial number of women who died after recurrence. Out of 618 deaths in the three treatment arms (Anastrozole, Tamoxifen and Combination), 389 of them (62.9%) occurred after recurrence. This indicated that recurrence could possibly quicken the occurrence of death. Furthermore, in a subsequent analysis of the trial data, there was a total of 831 deaths where 500 (60%) occurred after breast cancer recurrence and 331

(40%) without recurrence which was attributed to other causes[34]. The considerable proportion of deaths after recurrence suggests that the predictive value of relapse for death is high. In this scenario, regarding death as a non-informative censoring mechanism for recurrence is likely to lead to a bias in the estimation of recurrence-free survival. Thus, it will be crucial to treat censoring of recurrence by death as being dependent so as to provide an accurate estimation of recurrence-free survival.

Further, since the occurrence of death will inherently prevent any recurrence from being observed but not vice versa, a semi-competing risks data structure results. Techniques for analyzing this type of data will have to be adopted.

2.2 Hip fractures

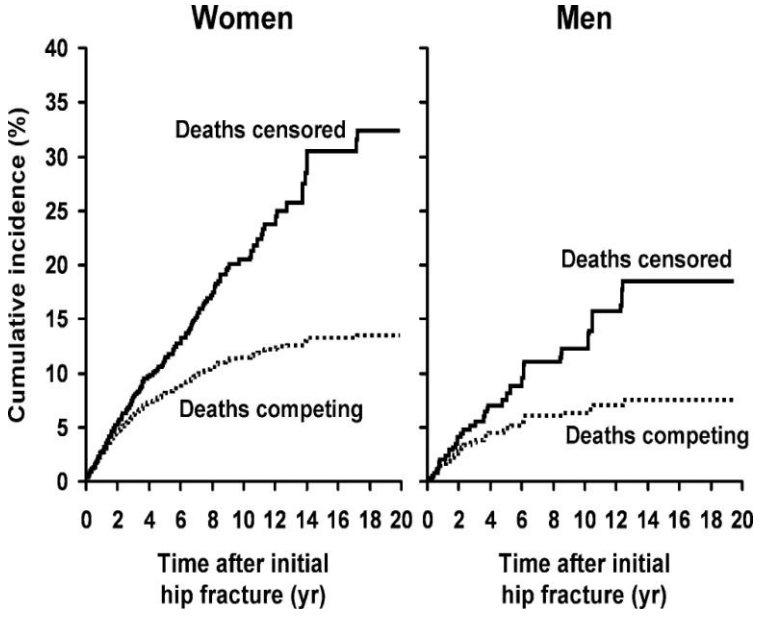
In a population-based study conducted to investigate the trend in recurrence of hip fractures, hip fractures that occurred among residents of the central city of Rochester from 1928 to 2006, and among residents of Olmsted County (including the rural areas) from 1980 to 2006 were identified via medical records linkage.[35]

The cumulative incidence of a second hip fracture was calculated among those with a first-ever hip fracture. In order to calculate the recurrence of hip fractures, 2 calculations were carried out in this study – the first which censored observation time upon death, and the second which treated death as a competing event. In addition, since fracture recurrence might be reduced among people treated with hip arthroplasty, observation time for these individuals was censored at the time an arthroplasty was performed.

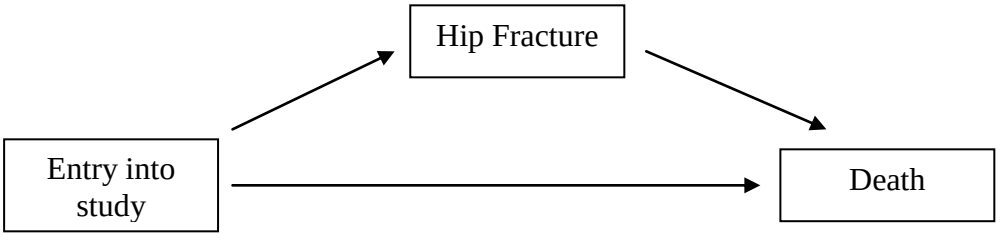
Out of 2434 patients (1832 women and 602 men) with a first-ever hip fracture, 219 patients experienced recurrent hip fractures over a follow-up period of 10000 person-years. The median time from the first to the second hip fracture was 2.7 years for all patients, 2.8 years for women and 2.1 years for men.

In the first analysis which censored observation time upon death, the cumulative incidence of a second hip fracture was 29% for all patients, 32% for women and 18% for men. However, it was noted that there was a high death rate among the patients, which could result in an overestimation of recurrence rate. Hence in order to obtain a more realistic estimate for recurrence rate, a second analysis was performed treating death as a competing event. In this analysis, the estimated cumulative incidence of a second hip fracture was 12% for all subjects, 13% for women and 7% for men.

Figure 4: Cumulative incidence of a recurrent hip fracture among 2434 patients who had a first-ever hip fracture in 1980–2006 with follow-up censored at death or with deaths treated as a competing risk[35]



Hip fracture as an intermediate event does not preclude death from occurring, but when death occurs, it will inherently preclude any further observation of hip fractures; thereby fitting into the semi-competing risks framework. Approaches for semi-competing risks do not impose any assumption, but explicitly model the disease progression from hip fracture to death. All causes of death can be accommodated regardless of whether it is related to recurrent hip fractures. A schema of how the data for hip fractures and death is able to fit into the semi-competing risks paradigm is illustrated as below.



2.3 AIDS

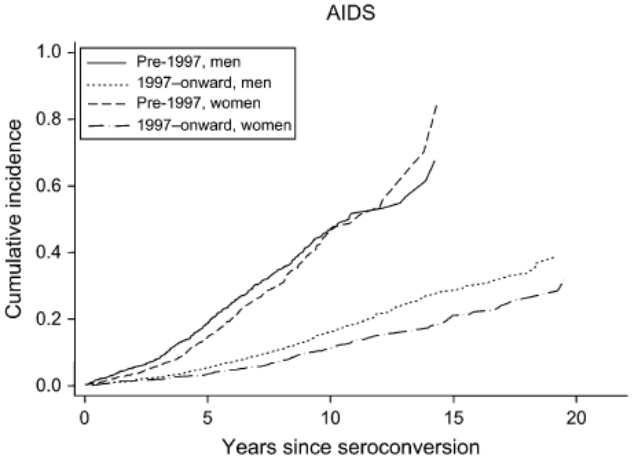
This example was derived from data of HIV-1 patients collected from the Concerted Action on SeroConversion to AIDS and Death in Europe (CASCADE).[36] The objective of the study was to assess the effect of gender on survival, progression to AIDS, as well as on the risk of developing each specific AIDS defining events (such as candidiasis, cryptococcosis, Kaposi's sarcoma, AIDS dementia complex, herpes simplex disease and HIV wasting syndrome) as first event and death without AIDS over time. The data was derived from a collaborative effort from 23 HIV seroconverter cohort studies in Europe, Australia and Canada. A total of 6923 subjects (3414 women and 3509 men) were entered into the study, where they were followed up from the latest of the three dates – seroconversion, entry into the cohort, and 1 December 1986.

In order to investigate the effect of sex on the progression to AIDS, as well as to each specific AIDS defining event as the event of interest, and death without AIDS as the competing event, modeling techniques involving cause-specific hazards and hazards of sub-distribution functions were used.

While there did not seem to be any gender differences in the progression to AIDS before 1997, females had a 24% (95% CI: 10 - 37) lower risk of developing AIDS as compared to the males after 1997, after adjusting for potential confounders - drug use via injections, sexual activity and age at seroconversion (Figure 5). Before 1997, there did not appear to be a prognostic value of gender on

the risk of each specific AIDS defining event or death without AIDS, except for Kaposi's sarcoma where it was shown that females had a lower risk of developing the disease. After 1997, it was observed that females were at a lower risk of developing AIDS dementia complex, tuberculosis, Kaposi's sarcoma and lymphomas. Throughout the study period, females were at a lower risk of death without AIDS than men.

Figure 5: Cumulative incidence of AIDS, stratified by calendar period (pre-1997 and 1997–2006) and gender, CASCADE collaboration.[36]



In this study, competing risks analyses were used in the examination of the progression to AIDS, AIDS defining events and death without AIDS. However, it was noted that the occurrence of death after AIDS have been captured in the CASCADE study. Thus, it will be interesting to see how covariate effects compare in terms of the prognostic outlook before and after the development of AIDS (or AIDS defining events). Although AIDS, AIDS defining event and death were outcomes which have been captured in the study, the manner in which these

outcomes relate to one another, such as the predictiveness of AIDS (or AIDS defining event) on death, has not been assessed. Hence, a semi-competing risks approach can be used to analyze the progression to AIDS, taking into account possible dependent censoring by all-cause mortality.

Chapter 3: Parametric modeling of semi-competing risks outcomes

In this chapter, we describe a new method for analyzing semi-competing risks data. A compartment model approach is proposed to describe survival experiences and to examine the effect of each prognostic factor for each possible endpoint encountered in a disease progression pathway, and to estimate the correlation between any two event types (non-terminal and terminal) for each subject. To facilitate the discussion of the proposed method, we assume that the only outcomes that can arise are relapse (non-terminal) and death (terminal). Without loss of generality, we also assume that there is only a single covariate of interest (treatment) in the discussion of our proposed methodology.

3.1 Compartment model

For subject n, where $n = 1, ..., N$, let $Y_{1,n}$ and $Y_{2,n}$ be the time to non-terminal and terminal events respectively,. Both times are measured from the time since entry into the study to the occurrence of each event. By convention, we allow $Y_{1,n}$ to take on the value of infinity if the non-terminal event does not occur prior to death. The administrative censoring time is denoted by C_n and the treatment covariate by x_n. The observations consist of $T_{2,n} = \min(Y_{2,n}, C_n)$, $T_{1,n} = \min(Y_{1,n},T_{2,n})$, $\delta_{2,n} = I(Y_{2,n} \leq C_n)$, $\delta_{1,n} = I(Y_{1,n} \leq T_{2,n})$ and x_n, for $n = 1, \ldots, N$. $I(.)$

is an indicator function which takes on values 1 if the event occurs and 0 otherwise.

In order to characterize the correlation between morbidity and mortality for each individual in the proposed compartment model, semi-competing risks data are analyzed using frailty models, where the frailty is denoted by *w*. The frailties are assumed to be independently and identically distributed with probability density function (pdf) $g_\theta(w)$, which follows a gamma distribution with mean 1 and variance θ. Note that the mean is set to be 1 to avoid the problem of non-identifiability.

$$g_\theta(w) = \frac{1}{\Gamma(\frac{1}{\theta})}\theta^{-\frac{1}{\theta}} w^{\frac{1}{\theta}-1} e^{-\frac{\omega}{\theta}}, \quad \theta \geq 0$$

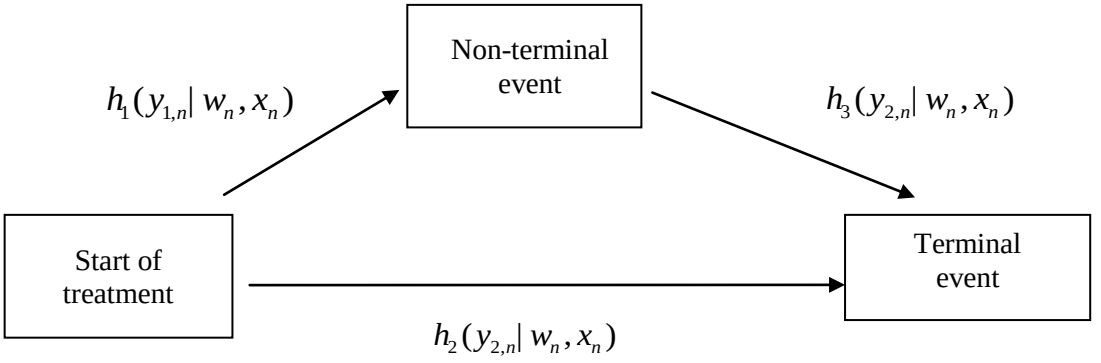
θ could be re-parameterized into $e^{\theta'}$ to ensure that θ is strictly non-negative. The gamma density function for *w* is written as:

$$g_{\theta'}(w) = \frac{1}{\Gamma(e^{-\theta'})}(e^{\theta'})^{-e^{-\theta'}} w^{e^{-\theta'}-1} e^{-\omega e^{-\theta'}}$$

In this case, $g_{\theta'}(w)$ follows a gamma distribution with mean = 1 and variance = $e^{\theta'}$.

Although the gamma frailty is used here, other frailty models could also be used in the framework of the proposed method. In this scenario, the popular gamma frailty model is assumed because of its mathematical convenience.

The compartment model shown below is used to describe the disease process. Given ω_n, we assume that for the n^{th} individual, the conditional hazards of the 3 paths are of the following forms:



(i) Hazard for non-terminal event

$$\begin{aligned} h_1(y_{1,n}|\, w_n, x_n) &= h_{01}(y_{1,n} \mid w_n) exp(\beta_1^T x_n) \\ &= \{\lim_{h->0} \frac{1}{h} \Pr(y_{1,n} \le Y_{1,n} \le y_{1,n} + h \mid Y_{1,n} \ge y_{1,n}, Y_{2,n} \ge y_{1,n}, w_n)\} exp(\beta_1^T x_n) \\ &= h_{01}(y_{1,n}) \omega_n \, exp(\beta_1^T x_n), \quad y_{1,n} \ge 0 \end{aligned}$$

(ii) Hazard for terminal event without prior occurrence of non-terminal event

$$\begin{aligned} h_2(y_{2,n}|\, w_n, x_n) &= h_{02}(y_{2,n} \mid w_n) exp(\beta_2^T x_n) \\ &= \{\lim_{h->0} \frac{1}{h} \Pr(y_{2,n} \le Y_{2,n} \le y_{2,n} + h \mid Y_{1,n} \ge y_{2,n}, Y_{2,n} \ge y_{2,n}, w_n)\} exp(\beta_2^T x_n), \\ &= h_{02}(y_{2,n}) \omega_n \, exp(\beta_2^T x_n), \quad y_{2,n} \ge 0 \end{aligned}$$

(iii) Hazard for terminal event following the occurrence of a non-terminal event

$$\begin{aligned} h_3(y_{2,n}|\, y_{1,n}, w_n, x_n) &= h_{03}(y_{2,n}|\, y_{1,n}, w_n) exp(\beta_3^T x_n) \\ &= \{\lim_{h->0} \frac{1}{h} \Pr(y_{2,n} \le Y_{2,n} \le y_{2,n} + h \mid Y_{1,n} = y_{1,n}, Y_{2,n} \ge y_{1,n}, w_n)\} exp(\beta_3^T x_n) \\ &= h_{03}(y_{2,n}) \omega_n \, exp(\beta_3^T x_n), \quad y_{2,n} \ge y_{1,n} \ge 0 \end{aligned}$$

In the above formulation, the covariate effect is incorporated through the Cox proportional hazards model for all 3 paths of the compartment model, with β representing the regression coefficient associated with the covariate vector x_n. The baseline hazard associated with the non-terminal event is denoted by h_{01}; and the baseline hazards associated with the terminal event without or after the occurrence of a non-terminal event are denoted by h_{02} and h_{03} respectively. Under this circumstance, it is assumed that frailty is unable to fully characterize the dependency between two very different types of events, namely relapse and death. Hence, a more general model, which accounts for possibly differing hazards of death depending on whether there was a prior occurrence of relapse ($\beta_2 \neq \beta_3$ and $h_{02} \neq h_{03}$), is used. We coin this as the "General compartment model".

When frailty fully accounts for the dependency between relapse and death ($\beta_2 = \beta_3$ and $h_{02} = h_{03}$), a "Restrictive compartment model" results. This is assumed by previous approaches which may not be valid in practice.[7,18]

In this thesis, we discuss primarily the methodology of a General compartment model, since the Restrictive model is a special case of the former. The validity of a Restrictive model may also be assessed by testing if $\beta_2 = \beta_3$ and $h_{02} = h_{03}$ simultaneously in the General compartment model using the likelihood ratio test.

In the General compartment model, the baseline hazard functions h_{01}, h_{02} and h_{03} are assumed to be of Weibull form due to its wide applicability and

flexibility for survival data. We allowed h_{01}, h_{02} and h_{03} to have different shape (γ) and scale (λ) parameters. To be more specific, the baseline hazard functions together with their respective cumulatives are defined as:

$$h_{01}(y_1) = \lambda_1\gamma_1(\lambda_1 y_1)^{\gamma_1 - 1}, \quad H_{01}(y_1) = (\lambda_1 y_1)^{\gamma_1};$$

$$h_{02}(y_2) = \lambda_2\gamma_2(\lambda_2 y_2)^{\gamma_2 - 1}, \quad H_{02}(y_2) = (\lambda_2 y_2)^{\gamma_2};$$

$$h_{03}(y_2) = \lambda_3\gamma_3(\lambda_3 y_2)^{\gamma_3 - 1}, \quad H_{03}(y_2) = (\lambda_3 y_2)^{\gamma_3} \qquad \text{(A)}$$

The hazard is monotonically decreasing for $\gamma < 1$, increasing for $\gamma > 1$ and constant for $\gamma = 1$. The exponential distribution is a special case of the Weibull distribution when both λ and γ are equal to 1. Similar to the re-parameterization of θ, λs and γs can also be re-parameterized into $e^{\lambda'}$ and $e^{\gamma'}$ to ensure that the scale and shape parameters are non-negative. Then, the formulations in (A) will become

$$h_{01}(y_1) = e^{\gamma_1'} e^{\lambda_1'} (e^{\lambda_1'} y_1)^{e^{\gamma_1'} - 1}, \quad H_{01}(y_1) = (e^{\lambda_1'} y_1)^{e^{\gamma_1'}};$$

$$h_{02}(y_2) = e^{\gamma_2'} e^{\lambda_2'} (e^{\lambda_2'} y_2)^{e^{\gamma_2'} - 1}, \quad H_{02}(y_2) = (e^{\lambda_2'} y_2)^{e^{\gamma_2'}};$$

$$h_{03}(y_2) = e^{\gamma_3'} e^{\lambda_3'} (e^{\lambda_3'} y_2)^{e^{\gamma_3'} - 1}, \quad H_{03}(y_2) = (e^{\lambda_3'} y_2)^{e^{\gamma_3'}}$$

3.2 Likelihood estimation and algorithm

Define $S_1(t_{1,n}\,|w_n, x_n) = \exp\{-H_1(t_{1,n}\,|w_n, x_n)\}$,

$S_2(t_{1,n}\,|w_n, x_n) = \exp\{-H_2(t_{1,n}\,|w_n, x_n)\}$ and

$S_3(t_{2,n}\mid t_{1,n}, w_n, x_n) = \exp(-(H_{03}(t_{2,n}) - H_{03}(t_{1,n}))w_n exp(\beta_3^{\,T} x_n))$, where t_1 and t_2 are the observed times.

Conditional on the frailty w_n, the likelihood $L(\lambda, \beta, \gamma| w, x)$ from the observations $\{(t_{1,n}, t_{2,n}, \delta_{1,n}, \delta_{2,n}, x_n), n = 1, \ldots, N\}$ is

$$\prod_{n=1}^{N}\left(h_1(t_{1,n}|w_n, x_n)\right)^{\delta_{1,n}}\left(h_2(t_{2,n}\,|w_n, x_n)\right)^{(1-\delta_{1,n})\delta_{2,n}}\left(h_3(t_{2,n}\,|t_{1,n}, w_n, x_n)\right)^{\delta_{1,n}\delta_{2,n}}$$
$$\times\; S_1(t_{1,n}\,|w_n, x_n)S_2(t_{1,n}\,|w_n, x_n)S_3(t_{2,n}\,|t_{1,n}, w_n, x_n)$$
$$=\prod_{n=1}^{N}\left(w_n h_{01}(t_{1,n})exp(\beta_1^{\,T} x_n)\right)^{\delta_{1,n}}\left(w_n h_{02}(t_{2,n})exp(\beta_2^{\,T} x_n)\right)^{(1-\delta_{1,n})\delta_{2,n}}\left(w_n h_{03}(t_{2,n})exp(\beta_3^{\,T} x_n)\right)^{\delta_{1,n}\delta_{2,n}}$$
$$\times\; \exp(-w_n H_{01}(t_{1,n})exp(\beta_1^{\,T} x_n))\exp(-w_n H_{02}(t_{1,n})exp(\beta_2^{\,T} x_n))\exp(-(H_{03}(t_{2,n}) - H_{03}(t_{1,n}))w_n exp(\beta_3^{\,T} x_n)) \quad \textbf{(1)}$$

Denote the parameters to be estimated by $\boldsymbol{\eta} = (\theta, \lambda_1, \gamma_1, \beta_1, \lambda_2, \gamma_2, \beta_2, \lambda_3, \gamma_3, \beta_3)$.

If the w_n's could be observed, the logarithm of the complete data likelihood is

$$\log L_{complete}(\eta;\ data, w_1,\ ..,\ w_N)$$

$$= \log\{L(\lambda,\ \beta,\ \gamma \mid w,\ x)\prod_{n=1}^{N} g_\theta(w_n)\}$$

$$= \log\{\prod_{n=1}^{N}\left(w_n h_{01}(t_{1,n})exp(\beta_1^T x_n)\right)^{\delta_{1,n}}\left(w_n h_{02}(t_{2,n})exp(\beta_2^T x_n)\right)^{(1-\delta_{1,n})\delta_{2,n}}\left(w_n h_{03}(t_{2,n})exp(\beta_3^T x_n)\right)^{\delta_{1,n}\delta_{2,n}}$$

$$\times\ \exp(-w_n H_{01}(t_{1,n})\ exp(\beta_1^T x_n))\exp(-w_n H_{02}(t_{1,n})\ exp(\beta_2^T x_n))$$

$$\times\ \exp(-(H_{03}(t_{2,n}) - H_{03}(t_{1,n}))\ w_n\ exp(\beta_3^T x_n))$$

$$\times\ \frac{1}{\Gamma(\frac{1}{\theta})}\theta^{-\frac{1}{\theta}} w^{\frac{1}{\theta}-1} e^{-\frac{w}{\theta}}\}$$

$$= -N\log(\Gamma(\frac{1}{\theta})) - \frac{N}{\theta}\log\theta$$

$$+\sum_{n=1}^{N}\{(\frac{1}{\theta}-1)\log w_n\ -\ \frac{w_n}{\theta}\ +\ \delta_{1,n}\log(w_n h_{01}(t_{1,n}))\ +\ \delta_{1,n}\beta_1^T x_n\ +\ (1-\delta_{1,n})\delta_{2,n}\log(w_n h_{02}(t_{2,n}))$$

$$+(1-\delta_{1,n})\delta_{2,n}\beta_2^T x_n + \delta_{1,n}\delta_{2,n}\log(w_n h_{03}(t_{2,n}))\ +\ \delta_{1,n}\delta_{2,n}\beta_3^T x_n$$

$$-\ w_n H_{01}(t_{1,n})exp(\beta_1^T x_n) - w_n H_{02}(t_{1,n})exp(\beta_2^T x_n) - (H_{03}(t_{2,n}) - H_{03}(t_{1,n}))w_n exp(\beta_3^T x_n)\}$$

(2)

Both the Newton-Raphson (NR) and the Expectation-Maximization (EM) algorithms can be used for parameter estimation.[37] NR, which is the method adopted to compute parameter estimates in this thesis, is elaborated as follows.

3.2.1 Newton-Raphson method

The Newton-Raphson (NR) method aims to find estimates that maximize the observed full likelihood of the data. Under our current model framework, the

observed full likelihood can be obtained after integrating the complete data likelihood over the space of the frailty variable w_n. The observed full likelihood $L_{full}(\eta \mid data)$ is

$$
\begin{aligned}
& L_{full}(\eta \mid data) \\
&= \int L_{complete}(\eta; data, w_1, ..., w_n)\, dw \\
&= \int L(\lambda, \beta, \gamma \mid w, x)\, g_\theta(w)\, dw \\
&= \int \prod_{n=1}^{N} \left(h_1(t_{1,n} \mid w_n, x_n) \right)^{\delta_{1,n}} \left(h_2(t_{2,n} \mid w_n, x_n) \right)^{(1-\delta_{1,n})\delta_{2,n}} \left(h_3(t_{2,n} \mid t_{1,n}, w_n, x_n) \right)^{\delta_{1,n}\delta_{2,n}} \\
&\quad \times \exp(-w_n H_{01}(t_{1,n}) exp(\beta_1^T x_n)) \exp(-w_n H_{02}(t_{1,n}) exp(\beta_2^T x_n)) \exp(-(H_{03}(t_{2,n}) - H_{03}(t_{1,n})) w_n exp(\beta_3^T x_n)) \\
&\quad \times \frac{1}{\Gamma(\frac{1}{\theta})} \theta^{-\frac{1}{\theta}} w_n^{\frac{1}{\theta}-1} e^{-\frac{w_n}{\theta}}\, dw \\
&= \prod_{n=1}^{N} \left(h_{01}(t_{1,n}) exp(\beta_1^T x_n) \right)^{\delta_{1,n}} \left(h_{02}(t_{2,n}) exp(\beta_2^T x_n) \right)^{(1-\delta_{1,n})\delta_{2,n}} \left(h_{03}(t_{2,n}) exp(\beta_3^T x_n) \right)^{\delta_{1,n}\delta_{2,n}} \\
&\quad \times (1+\theta)^{\delta_{1,n}\delta_{2,n}} \{1 + \theta[H_{01}(t_{1,n}) exp(\beta_1^T x_n) + H_{02}(t_{1,n}) exp(\beta_2^T x_n) + [(H_{03}(t_{2,n}) - H_{03}(t_{1,n})] exp(\beta_3^T x_n))]\}^{-(\frac{1}{\theta} + \delta_{1,n} + \delta_{2,n})} \\
&= \prod_{n=1}^{N} \left(\lambda_1 \gamma_1 (\lambda_1 t_1)^{\gamma_1 - 1} exp(\beta_1^T x_n) \right)^{\delta_{1,n}} \left(\lambda_2 \gamma_2 (\lambda_2 t_2)^{\gamma_2 - 1} exp(\beta_2^T x_n) \right)^{(1-\delta_{1,n})\delta_{2,n}} \left(\lambda_3 \gamma_3 (\lambda_3 t_2)^{\gamma_3 - 1} exp(\beta_3^T x_n) \right)^{\delta_{1,n}\delta_{2,n}} \\
&\quad \times (1+\theta)^{\delta_{1,n}\delta_{2,n}} \{1 + \theta[(\lambda_1 t_1)^{\gamma_1} exp(\beta_1^T x_n) + (\lambda_2 t_1)^{\gamma_2} exp(\beta_2^T x_n) + [(\lambda_3 t_2)^{\gamma_3} - (\lambda_3 t_1)^{\gamma_3}] exp(\beta_3^T x_n))]\}^{-(\frac{1}{\theta} + \delta_{1,n} + \delta_{2,n})}
\end{aligned}
\qquad \textbf{(3)}
$$

After computing the observed full log-likelihood, $\frac{\partial}{\partial \eta} \log L_{full}(\eta)$ and $\frac{\partial^2}{\partial \eta^T \partial \eta} \log L_{full}(\eta)$ can be obtained by computing the row vector of first partial derivatives and matrix of second partial derivatives of $\log L_{full}(\eta)$ respectively. $\frac{\partial}{\partial \eta} \log L_{full}(\eta)$ is known as the score function and $\frac{\partial^2}{\partial \eta^T \partial \eta} \log L_{full}(\eta)$ as the observed

information matrix. Details for computing the score and information matrix can be found in the appendix. The estimate of $\boldsymbol{\eta}$ can then be iteratively obtained via

$$\eta^{(k+1)} = \eta^{(k)} + \left(-\frac{\partial^2}{\partial\eta^T\partial\eta}\log L_{full}(\eta)\Big|_{\eta^{(k)}}\right)^{-1}\left(\frac{\partial}{\partial\eta}\log L_{full}(\eta)\Big|_{\eta^{(k)}}\right)$$

where $\boldsymbol{\eta}^{(k+1)}$ and $\boldsymbol{\eta}^{(k)}$ are estimates obtained from the $(k+1)^{\text{th}}$ and k^{th} iteration respectively.

From the algorithm, the corresponding covariance matrix can also be obtained by taking the inverse of $U''(\eta) = -\frac{\partial^2}{\partial\eta^T\partial\eta}\log L_{full}(\lambda,\beta,\gamma,\theta)$ evaluated at the maximum likelihood estimates $\hat{\eta}$.

3.3 Model checking

3.3.1 Assessment of overall model adequacy

Estimation of the parameters will be valid if the model is correctly specified or is adequate. Overall model adequacy can be checked via graphical techniques. We propose a graphical model checking method based on Cox-Snell residuals. The idea behind Cox-Snell residuals is that if the model fits well, the estimated model-based cumulative hazard should behave like a censored sample from an exponential distribution with rate 1. They can be derived as follows.

Let $S(t)$ denote a survival function. Since $0 \leq S(t) \leq 1$, let $U = S(T)$. Therefore, $0 \leq U \leq 1$ and $T = S^{-1}(U)$. Since U is uniform in [0,1], -log(U) is exponential with rate 1. However, note that -log(U) = -log($S(T)$) = $H(T)$. Hence, $\hat{H}(T_n; x_n) = \hat{H}_0(T_n)\exp(\beta^T x_n)$ is the Cox-Snell residual for T_n for subject $n = 1, \ldots, N$. If the model is adequate, $\hat{H}(T_n; x_n)$ will behave like a censored sample from an exponential distribution with rate 1.[40]

Model checking is implemented for times to the non-terminal event, as well as that for the terminal event with or without the prior occurrence of the non-terminal event. Cox-Snell residuals are first obtained by computing their estimated cumulative hazards denoted by $r_{ni} = \hat{H}_i(.)$, for subject $n = 1, \ldots, N$ and type of event i = 1, 2, 3. The cumulative hazards can be derived from the respective marginal hazards $\hat{h}_i(.)$ as follows:

(i) Non-terminal event

$$
\begin{aligned}
\hat{h}_1(y_1) &= \frac{\Pr(Y_1 = y_1, Y_2 \geq y_1)}{\Pr(Y_1 \geq y_1, Y_2 \geq y_1)} \\
&= \frac{E_w\{\Pr(Y_1 = y_1, Y_2 \geq y_1 \mid w)\}}{E_w\{\Pr(Y_1 \geq y_1, Y_2 \geq y_1 \mid w)\}} \\
&= \frac{\int h_1(y_1 \mid w, x) e^{-H_1(y_1|w,x)} e^{-H_2(y_1|w,x)} g_\theta(w) dw}{\int e^{-H_1(y_1|w,x)} e^{-H_2(y_1|w,x)} g_\theta(w) dw} \\
&= \frac{\int w h_1(y_1) e^{-wH_1(y_1)} e^{-wH_2(y_1)} g_\theta(w) dw}{\int e^{-wH_1(y_1)} e^{-wH_2(y_1)} g_\theta(w) dw} \\
&= \frac{h_1(y_1) \int w^{(\frac{1}{\theta}+1)-1} e^{-w[\frac{1}{\theta}+H_1(y_1)+H_2(y_1)]} dw}{\int w^{\frac{1}{\theta}-1} e^{-w[\frac{1}{\theta}+H_1(y_1)+H_2(y_1)]} dw} \\
&= \frac{h_1(y_1)\Gamma(\frac{1}{\theta}+1)[\frac{1}{\frac{1}{\theta}+H_1(y_1)+H_2(y_1)}]^{\frac{1}{\theta}+1}}{\Gamma(\frac{1}{\theta})[\frac{1}{\frac{1}{\theta}+H_1(y_1)+H_2(y_1)}]^{\frac{1}{\theta}}} \\
&= \frac{h_1(y_1)}{1+\theta H_1(y_1)+\theta H_2(y_1)}, \qquad \textit{where} \quad y_1 \geq 0
\end{aligned}
$$

(ii) Terminal event without prior occurrence of non-terminal event

$$
\begin{aligned}
\hat{h}_2(y_2) &= \frac{\Pr(Y_1 \geq y_2, Y_2 = y_2)}{\Pr(Y_1 \geq y_2, Y_2 \geq y_2)} \\
&= \frac{E_w\{\Pr(Y_1 \geq y_2, Y_2 = y_2 \mid w)\}}{E_w\{\Pr(Y_1 \geq y_2, Y_2 \geq y_2 \mid w)\}} \\
&= \frac{\int h_2(y_2 \mid w, x) e^{-H_1(y_2|w,x)} e^{-H_2(y_2|w,x)} g_\theta(w) dw}{\int e^{-H_1(y_2|w,x)} e^{-H_2(y_2|w,x)} g_\theta(w) dw} \\
&= \frac{h_2(y_2)}{1+\theta H_1(y_2)+\theta H_2(y_2)}, \qquad \textit{where} \quad y_2 \geq 0
\end{aligned}
$$

(iii) Terminal event following the occurrence of a non-terminal event

$$\begin{aligned}
\hat{h}_3(y_2 \mid y_1) &= \frac{\Pr(Y_2 \geq y_1, Y_2 = y_2 \mid Y_1 = y_1)}{\Pr(Y_2 \geq y_1, Y_2 \geq y_2 \mid Y_1 = y_1)} \\
&= \frac{E_w\{\Pr(Y_2 \geq y_1, Y_2 = y_2 \mid Y_1 = y_1, w)\}}{E_w\{\Pr(Y_2 \geq y_2 \mid Y_1 = y_1, w)\}} \\
&= \frac{\int h_3(y_2 \mid y_1, w, x) e^{-H_3(y_2|y_1,w,x)} h_1(y_1 \mid w, x) e^{-H_1(y_1|w,x)} e^{-H_2(y_1|w,x)} g_\theta(w) dw}{\int h_1(y_1 \mid w, x) e^{-H_3(y_2|y_1,w,x)} e^{-H_1(y_1|w,x)} e^{-H_2(y_1|w,x)} g_\theta(w) dw} \\
&= \frac{\int w[h_3(y_2) - h_3(y_1)] e^{-w[H_3(y_2)-H_3(y_1)]} w h_1(y_1) e^{-wH_1(y_1)} e^{-wH_2(y_1)} g_\theta(w) dw}{\int w h_1(y_1) e^{-w[H_3(y_2)-H_3(y_1)]} e^{-wH_1(y_1)} e^{-wH_2(y_1)} g_\theta(w) dw} \\
&= \frac{(1+\theta)[h_3(y_2) - h_3(y_1)]}{1+\theta[H_3(y_2) - H_3(y_1) + H_1(y_1) + H_2(y_1)]}, \qquad \textit{where} \quad y_2 \geq y_1 \geq 0
\end{aligned}$$

Subsequently, the product-limit estimate of the cumulative hazard $\hat{H}(r_i)$ for each event i = 1, 2, 3 can be computed from the censored sample (r_{ni}, δ_{ni}). The plot of $\hat{H}(r_i)$ against r_i will approximately follow the 45^o line if the model is appropriate.

3.3.2 Choice of model

In order to determine whether a restrictive compartment model can be used in place of the general model, a likelihood ratio test can be used. As in Section 3.2, the parameter estimates in the general model are denoted by $\boldsymbol{\eta}$ = (θ, λ_1, γ_1, β_1, λ_2, γ_2, β_2, λ_3, γ_3, β_3). A test of whether a restrictive model is adequate is equivalent to testing whether $\beta_2 = \beta_3$, $\lambda_2 = \lambda_3$, and $\gamma_2 = \gamma_3$ (that is, $\beta_2 - \beta_3 = 0$, $\lambda_2 - \lambda_3 = 0$, and $\gamma_2 - \gamma_3 = 0$). This test can be carried out via the construction of contrasts.

The contrast matrix involving the 3 linear hypotheses is first written as $C = \begin{pmatrix} 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & -1 \\ 0 & 0 & 0 & 0 & 1 & 0 & 0 & -1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & -1 & 0 \end{pmatrix}$. After which, the likelihood ratio test is implemented using the test statistic $(C\hat{\eta} - d)^T (CV^{-1}C^T)(C\hat{\eta} - d)$, where $d = \begin{pmatrix} 0 \\ 0 \\ 0 \end{pmatrix}$ and $V = U''(\hat{\eta})$. The statistic follows a chi-square distribution with 3 degrees of freedom.

Chapter 4: Simulation Studies

4.1 Simulated data

Simulation studies were conducted to assess the performance of the proposed method under different scenarios. For simplicity, we assumed that there was only one explanatory variable, *treatment*, which was coded as 1 or 0. Sample sizes of N = 200 and 300 were considered in the simulation studies. The covariate *treatment* was generated from a binomial distribution of size N with probability 0.5; and Y_1 and Y_2 were generated from the compartment model in Section 3.1, where Y_1 represented the time to relapse and Y_2 represented the time to death. Throughout the simulation studies, the baseline hazard for relapse was of the form $h_{01}(y_1) = 2$ where λ_1 = 2 and γ_1 = 1. Similarly, the baseline hazard for death without relapse was of the form $h_{02}(y_2) = 2y_2$ where λ_2 = 1 and γ_2 = 2; and the baseline hazard for death after relapse (if applicable) was of the form $h_{03}(y_2) = 1$ where λ_3 = 1 and γ_3 = 1. An independent administrative censoring time C was generated from a uniform distribution ~ Uniform (0, τ), where τ was a value chosen to yield censoring proportions of 30% and 50%.

Under the above-mentioned simulation settings, we evaluated the performance of the proposed method for different magnitudes of dependency between relapse and death. The parameter θ, which is associated with the

dependence structure, was varied to take values 0.5 representing weak dependence between relapse and death, 1 indicating moderate positive dependence and 2 indicating large positive dependence. In addition, the performance of our model was evaluated under scenarios which considered an adverse, null or beneficial treatment effect on death. Under the general model formulation, we allowed the HR of relapse (denoted by $HR_{relapse} = \exp(\beta_1)$), and of death after relapse (denoted by $HR_{death\_after\_relapse} = \exp(\beta_3)$) to take on values 0.5 or 1. The HR of death without any observation of relapse (denoted by $HR_{death\_without\_relapse} = \exp(\beta_2)$) was varied to take on values 0.5, 1 or 2. Under the restrictive model formulation, the HR of death, denoted by $HR_{death} = \exp(\beta_2)$, takes on values 0.5, 1 or 2. The treatment effect on relapse, (denoted by $HR_{relapse} = \exp(\beta_1)$) was assigned values of 0.5 and 1.

The proposed approach was evaluated based on its bias, mean-squared error (MSE) and coverage probability (CP) at the nominal 95% level. For each simulation setting, 1000 replicates were generated. The MSEs were computed by taking the average of the squared bias resulting from the difference between the estimated and true parameter value. The coverage probability is the proportion of 95% confidence intervals which contains the true parameter value, out of 1000 replications.

4.2 Performance of proposed method

General Compartment Model:

Tables 3 to 6 present simulation results based on the General model obtained via NR algorithm, varying the effects of treatment on relapse ($HR_{relapse}$ = 0.5, 1), death without relapse ($HR_{death\_without\_relapse}$ = 0.5, 1, 2), or death after relapse ($HR_{death\_after\_relapse}$ = 0.5, 1).

When there is no treatment effect, that is $HR_{relapse}$ = $HR_{death\_without\_relapse}$ = $HR_{death\_after\_relapse}$ = 1, considering the simulation setting of n = 200 with 30% censoring, biases in the estimates are relatively close to zero as compared to the true parameter values with coverage probabilities approaching 95% for all degrees of dependence (θ) (Table 3).

Table 3: Simulation results obtained from the General compartment model varying θ, exp(β_1), exp(β_2) and exp(β_3) and constant $\lambda_1 = 2$, $\lambda_2 = 1$, $\lambda_3 = 1$, $\gamma_1 = 1$, $\gamma_2 = 2$, $\gamma_3 = 1$ for $n = 200$ with 30% censoring.

		$HR_{relapse} = 1$ $HR_{death\_without\_relapse} = 1$ $HR_{death\_after\_relapse} = 1$			$HR_{relapse} = 1$ $HR_{death\_without\_relapse} = 2$ $HR_{death\_after\_relapse} = 0.5$			$HR_{relapse}=1$ $HR_{death\_without\_relapse}=0.5$ $HR_{death\_after\_relapse}=0.5$			$HR_{relapse}=0.5$ $HR_{death\_without\_relapse}=1$ $HR_{death\_after\_relapse}=0.5$		
θ		**BIAS**	**MSE**	**CP(%)**	**BIAS**	**MSE**	**CP(%)**	**BIAS**	**MSE**	**CP(%)**	**BIAS**	**MSE**	**CP(%)**
0.5	θ	-0.072	0.247	94.9	-0.070	0.249	94.4	-0.054	0.196	95.4	-0.077	0.285	94.4
	β_1	0.006	0.047	95.4	0.005	0.048	95.5	0.004	0.046	95.9	-0.003	0.053	96.3
	β_2	-0.005	0.126	95.0	0.020	0.112	95.4	-0.021	0.147	95.7	-0.003	0.104	95.4
	β_3	-0.005	0.065	95.7	-0.018	0.078	95.1	-0.011	0.067	95.7	-0.018	0.092	95.5
	λ_1	-0.002	0.037	94.8	-0.003	0.036	95.0	-0.001	0.034	95.4	-0.002	0.038	94.4
	λ_2	0.003	0.030	93.9	0.002	0.029	94.5	0.003	0.026	95.1	0.003	0.030	94.5
	λ_3	0.025	0.041	96.6	0.025	0.042	96.5	0.022	0.038	96.3	0.029	0.043	96.5
	γ_1	0.015	0.010	94.9	0.014	0.011	94.6	0.013	0.009	95.2	0.015	0.012	94.9
	γ_2	0.056	0.066	94.8	0.052	0.061	94.2	0.060	0.069	94.8	0.055	0.064	94.0
	γ_3	0.017	0.027	94.9	0.017	0.027	93.9	0.015	0.023	94.0	0.018	0.031	94.3
1	θ	-0.002	0.086	95.4	-0.002	0.073	96.0	-0.007	0.076	95.2	-0.004	0.089	95.3
	β_1	0.003	0.070	93.4	0.002	0.073	93.9	0.004	0.069	93.2	-0.010	0.077	93.5
	β_2	0.003	0.156	94.5	0.032	0.144	94.7	-0.013	0.180	95.4	0.001	0.139	94.3
	β_3	0.021	0.089	94.7	0.004	0.101	94.6	0.006	0.087	95.3	-0.002	0.118	94.5
	λ_1	0.009	0.053	94.5	0.008	0.052	93.4	0.004	0.051	94.8	0.009	0.055	93.1
	λ_2	0.005	0.036	94.7	0.003	0.034	94.7	0.000	0.033	94.8	0.004	0.037	94.1
	λ_3	0.002	0.051	94.1	0.000	0.050	93.7	0.002	0.049	93.8	0.003	0.052	93.8
	γ_1	0.024	0.012	95.5	0.022	0.011	96.4	0.021	0.011	95.3	0.025	0.013	94.9
	γ_2	0.056	0.057	95.2	0.056	0.053	96.0	0.051	0.057	95.9	0.058	0.056	95.1
	γ_3	0.029	0.026	95.1	0.032	0.025	94.1	0.026	0.021	95.2	0.037	0.030	94.8
2	θ	0.014	0.046	94.1	0.016	0.046	94.2	0.016	0.039	95.4	0.018	0.051	93.7
	β_1	0.012	0.107	95.0	0.012	0.110	95.2	0.011	0.104	95.3	-0.004	0.116	95.7
	β_2	0.013	0.190	95.0	0.037	0.184	95.9	-0.010	0.212	94.7	0.017	0.180	95.3
	β_3	0.023	0.117	95.1	0.004	0.130	95.9	0.010	0.115	95.7	0.000	0.146	95.1
	λ_1	0.016	0.075	95.5	0.017	0.073	95.8	0.015	0.069	95.5	0.020	0.076	95.7
	λ_2	0.006	0.044	94.8	0.007	0.043	94.4	0.006	0.038	95.8	0.009	0.045	93.8
	λ_3	-0.002	0.057	95.4	-0.001	0.058	95.2	-0.004	0.057	94.7	0.001	0.059	95.6
	γ_1	0.027	0.015	94.7	0.027	0.015	94.8	0.025	0.013	95.0	0.030	0.017	94.9
	γ_2	0.056	0.060	94.2	0.053	0.055	95.1	0.057	0.055	94.5	0.059	0.056	95.6
	γ_3	0.030	0.024	94.6	0.031	0.024	94.3	0.028	0.021	95.6	0.035	0.029	94.6

In particular, large MSEs for θ, ranging from 0.196 to 0.285, are observed when θ = 0.5. However, the MSE decreases as θ increases. The CPs of all parameters remain relatively close to the nominal level of 95% for all values of θ considered. A large bias in the association parameter θ is also noted especially when there is a weak/ moderate association between the terminal and non-terminal events. This bias in the association parameter θ is most likely due to the fewer number of observations, and hence lesser amount of information, used to estimate θ when the association is weaker. However, the bias in θ decreases with an increase in sample size, as shown in Tables 3 to 6. Convergence problem was not encountered in the simulation studies and real data application.

When θ increases, there seem to be increases in MSEs for β_1 and β_3, with MSEs for β_2 remaining relatively substantial. In particular, the increase in MSEs seems to have been contributed by an increase in variance of the covariates. Generally, when θ increases from 0.5 to 2, the standard errors for βs increase from 0.2 to 0.4. The increase in standard errors in the βs is most likely influenced by the degree of dependence between the terminal and non-terminal events. There is no 1-to-1 relationship between the βs and θ. Instead, it is mediated by the number of observations and the influence of θ on the βs. An increase in dependence increases the difficulty in estimating βs, as it brings about an additional source of variability. In the extreme case where there is zero dependence between the different event types, the βs would have been independent. Therefore, estimation of βs in such instances will be more straightforward, without the need to account for an extra source of variation in the parameter estimation.

With substantial association between relapse and death, the proportion of deaths occurring with prior relapse is usually large (in our study, it is about 70%). Not accounting for informative censoring of relapse by death is expected to produce biases in the estimates relating to relapse.

In the same table (Table 3), it was shown that even when treatment has an effect on the risk of relapse, and death with or without prior relapse, the trends and magnitudes of the biases and MSEs of the parameter estimates are fairly similar to that observed when $HR_{relapse} = HR_{death\_without\_relapse} = HR_{death\_after\_relapse} = 1$.

With the exception of θ, conclusions drawn with regards to the biases and MSEs of β_1, β_2 and β_3 do not change, when the proportion of censoring increased from 30% to 50% (Table 4). Under all simulation settings, a rather large MSE of θ, ranging from 0.442 to 0.661, was observed under weak dependence. These MSEs were considerably larger than those obtained when the proportion of censored observations was 30%. Also, the 95% coverage was not reached – it ranged from 92.9% to 93.9%. However, a decreasing MSE for θ, together with CP approximating the 95% nominal level, is observed as θ increases.

Table 4: Simulation results obtained from the General compartment model varying θ, exp(β_1), exp(β_2) and exp(β_3) and constant $\lambda_1 = 2$, $\lambda_2 = 1$, $\lambda_3 = 1$, $\gamma_1 = 1$, $\gamma_2 = 2$, $\gamma_3 = 1$ for $n = 200$ with 50% censoring.

		$HR_{relapse} = 1$ $HR_{death\_without\_relapse} = 1$ $HR_{death\_after\_relapse} = 1$			$HR_{relapse} = 1$ $HR_{death\_without\_relapse} = 2$ $HR_{death\_after\_relapse} = 0.5$			$HR_{relapse}=1$ $HR_{death\_without\_relapse}=0.5$ $HR_{death\_after\_relapse}=0.5$			$HR_{relapse}=0.5$ $HR_{death\_without\_relapse}=1$ $HR_{death\_after\_relapse}=0.5$		
θ		**BIAS**	**MSE**	**CP(%)**	**BIAS**	**MSE**	**CP(%)**	**BIAS**	**MSE**	**CP(%)**	**BIAS**	**MSE**	**CP(%)**
0.5	θ	-0.131	0.626	93.9	-0.119	0.563	93.4	-0.097	0.442	93.7	-0.123	0.661	92.9
	β_1	0.007	0.051	95.1	0.006	0.052	95.6	0.004	0.050	95.3	-0.009	0.059	95.6
	β_2	-0.011	0.154	95.5	0.020	0.131	96.5	-0.035	0.183	95.9	-0.016	0.123	96.6
	β_3	-0.007	0.086	95.6	-0.028	0.106	95.7	-0.020	0.085	95.5	-0.036	0.130	95.7
	λ_1	0.005	0.048	94.4	0.004	0.046	94.3	0.004	0.043	94.6	0.010	0.048	95.3
	λ_2	0.011	0.041	95.1	0.010	0.040	94.5	0.008	0.036	94.4	0.016	0.041	94.5
	λ_3	0.033	0.053	96.9	0.032	0.053	97.2	0.031	0.046	96.8	0.038	0.058	96.8
	γ_1	0.021	0.014	94.3	0.020	0.014	93.6	0.019	0.012	94.4	0.024	0.016	93.7
	γ_2	0.073	0.091	94.3	0.069	0.082	95.1	0.071	0.091	94.7	0.074	0.084	95.5
	γ_3	0.027	0.042	92.7	0.025	0.043	94.1	0.021	0.034	94.6	0.030	0.051	93.8
1	θ	-0.014	0.166	93.9	-0.008	0.153	93.3	-0.013	0.138	94.1	-0.010	0.176	93.0
	β_1	0.001	0.076	94.0	0.000	0.077	95.1	0.000	0.073	93.8	-0.018	0.085	94.3
	β_2	0.008	0.189	94.5	0.031	0.174	95.0	-0.016	0.216	95.4	-0.001	0.165	95.7
	β_3	0.022	0.107	95.0	0.002	0.124	95.7	0.008	0.105	95.3	-0.006	0.144	96.0
	λ_1	0.014	0.070	94.1	0.014	0.068	93.4	0.011	0.064	94.2	0.018	0.072	93.5
	λ_2	0.003	0.054	94.3	0.005	0.051	94.1	0.002	0.047	94.6	0.009	0.053	94.5
	λ_3	0.011	0.061	95.0	0.009	0.059	94.9	0.004	0.056	94.7	0.012	0.066	94.6
	γ_1	0.029	0.015	95.4	0.028	0.015	95.1	0.026	0.014	94.8	0.032	0.017	95.3
	γ_2	0.064	0.084	95.8	0.062	0.075	95.7	0.059	0.080	96.3	0.069	0.077	96.2
	γ_3	0.035	0.039	95.2	0.037	0.041	95.2	0.031	0.034	95.1	0.040	0.046	94.6
2	θ	0.017	0.063	95.1	0.019	0.073	94.4	0.014	0.063	94.5	0.023	0.081	94.2
	β_1	0.012	0.110	96.0	0.012	0.116	95.5	0.010	0.110	95.3	-0.008	0.122	95.3
	β_2	0.020	0.215	95.3	0.043	0.218	95.3	-0.016	0.257	95.5	0.016	0.211	94.8
	β_3	0.025	0.130	95.6	0.005	0.157	94.7	0.010	0.130	95.6	-0.003	0.176	95.2
	λ_1	0.021	0.081	95.1	0.024	0.088	94.2	0.019	0.080	95.3	0.030	0.092	94.6
	λ_2	0.005	0.053	94.3	0.008	0.059	94.5	0.003	0.052	95.1	0.013	0.061	94.6
	λ_3	0.001	0.063	95.5	0.005	0.065	96.1	0.002	0.062	95.8	0.007	0.065	96.3
	γ_1	0.031	0.017	94.4	0.033	0.018	94.5	0.029	0.016	93.9	0.037	0.020	95.2
	γ_2	0.064	0.077	95.2	0.065	0.080	94.6	0.063	0.082	94.1	0.071	0.079	94.7
	γ_3	0.035	0.032	94.2	0.034	0.036	94.6	0.035	0.032	94.5	0.041	0.041	94.9

Increasing the sample size from $n = 200$ to $n = 300$ improves the precision of the parameter estimates. In general, biases for all estimates are even closer to zero with the increase in sample size. Additionally, a notable decrease in MSEs of the estimates are observed. The 95% coverage probability is also reached for almost all estimates (Tables 5 and 6).

Table 5: Simulation results obtained from the General compartment model varying θ, exp(β_1), exp(β_2) and exp(β_3), and constant $\lambda_1 = 2$, $\lambda_2 = 1$, $\lambda_3 = 1$, $\gamma_1 = 1$, $\gamma_2 = 2$, $\gamma_3 = 1$ for $n = 300$ with 30% censoring.

		$HR_{relapse} = 1$ $HR_{death\_without\_relapse} = 1$ $HR_{death\_after\_relapse} = 1$			$HR_{relapse} = 1$ $HR_{death\_without\_relapse} = 2$ $HR_{death\_after\_relapse} = 0.5$			$HR_{relapse}=1$ $HR_{death\_without\_relapse}=0.5$ $HR_{death\_after\_relapse}=0.5$			$HR_{relapse}=0.5$ $HR_{death\_without\_relapse}=1$ $HR_{death\_after\_relapse}=0.5$		
θ		**BIAS**	**MSE**	**CP(%)**	**BIAS**	**MSE**	**CP(%)**	**BIAS**	**MSE**	**CP(%)**	**BIAS**	**MSE**	**CP(%)**
0.5	θ	-0.027	0.125	96.3	-0.028	0.107	96.5	-0.023	0.104	95.5	-0.024	0.114	96.6
	β_1	-0.001	0.033	94.8	-0.001	0.035	94.9	-0.002	0.033	94.7	-0.008	0.038	94.6
	β_2	-0.007	0.082	94.3	0.004	0.073	95.2	-0.025	0.100	95.6	-0.004	0.071	94.4
	β_3	0.000	0.046	94.4	-0.007	0.053	94.7	-0.010	0.045	95.2	-0.014	0.061	95.0
	λ_1	0.004	0.023	95.1	0.001	0.023	95.0	0.003	0.023	94.2	0.003	0.023	95.6
	λ_2	0.002	0.020	94.5	0.001	0.020	94.7	0.003	0.019	94.9	0.003	0.019	94.7
	λ_3	0.010	0.027	94.5	0.010	0.028	94.6	0.010	0.026	94.3	0.012	0.028	94.8
	γ_1	0.010	0.007	95.3	0.009	0.007	95.0	0.009	0.006	95.8	0.010	0.007	95.4
	γ_2	0.035	0.042	94.9	0.031	0.036	96.1	0.040	0.043	94.8	0.033	0.033	96.2
	γ_3	0.016	0.016	96.1	0.017	0.016	95.6	0.014	0.014	95.7	0.019	0.018	96.0
1	θ	0.003	0.054	93.6	0.002	0.049	94.3	0.001	0.048	93.8	-0.002	0.057	94.5
	β_1	0.014	0.041	95.3	0.013	0.042	94.9	0.014	0.040	95.7	0.005	0.047	95.9
	β_2	0.004	0.096	95.4	0.016	0.088	96.0	-0.013	0.109	95.3	-0.001	0.084	95.7
	β_3	0.015	0.057	95.0	0.010	0.065	95.1	0.004	0.055	95.2	0.004	0.079	95.0
	λ_1	-0.001	0.033	94.9	-0.002	0.032	95.1	-0.002	0.031	95.1	-0.003	0.035	94.5
	λ_2	0.005	0.023	94.9	0.004	0.021	95.4	0.004	0.021	94.7	0.004	0.023	94.7
	λ_3	-0.001	0.029	96.7	-0.002	0.029	96.7	-0.001	0.028	97.0	-0.001	0.029	96.7
	γ_1	0.016	0.008	95.1	0.014	0.008	95.0	0.015	0.007	95.1	0.015	0.009	94.7
	γ_2	0.042	0.039	95.2	0.041	0.037	95.1	0.039	0.038	94.2	0.039	0.039	94.6
	γ_3	0.020	0.017	95.2	0.020	0.016	94.4	0.017	0.015	94.5	0.021	0.019	94.7
2	θ	0.011	0.033	93.6	0.017	0.031	93.2	0.008	0.029	93.6	0.015	0.035	92.8
	β_1	0.009	0.068	94.9	0.011	0.070	94.7	0.008	0.067	94.5	-0.003	0.073	94.9
	β_2	-0.005	0.130	95.2	0.015	0.127	95.8	-0.016	0.138	94.4	-0.006	0.118	94.8
	β_3	0.001	0.090	93.4	-0.012	0.097	93.9	-0.009	0.086	93.7	-0.016	0.107	94.2
	λ_1	0.009	0.053	95.3	0.012	0.053	94.8	0.006	0.050	95.5	0.011	0.055	93.9
	λ_2	0.012	0.028	94.7	0.014	0.028	94.3	0.009	0.026	95.1	0.014	0.030	94.2
	λ_3	0.010	0.041	94.1	0.010	0.041	93.7	0.007	0.041	94.1	0.011	0.042	94.4
	γ_1	0.019	0.009	94.8	0.022	0.010	93.9	0.017	0.009	94.4	0.022	0.011	94.5
	γ_2	0.043	0.034	95.7	0.050	0.035	95.0	0.041	0.032	95.5	0.049	0.038	94.5
	γ_3	0.018	0.016	95.0	0.018	0.015	95.0	0.015	0.013	94.6	0.020	0.018	95.4

Table 6: Simulation results obtained from the General compartment model varying θ, exp(β_1), exp(β_2) and exp(β_3), and constant $\lambda_1 = 2$, $\lambda_2 = 1$, $\lambda_3 = 1$, $\gamma_1 = 1$, $\gamma_2 = 2$, $\gamma_3 = 1$ for $n = 300$ with 50% censoring.

		$HR_{relapse} = 1$ $HR_{death\_without\_relapse} = 1$ $HR_{death\_after\_relapse} = 1$			$HR_{relapse} = 1$ $HR_{death\_without\_relapse} = 2$ $HR_{death\_after\_relapse} = 0.5$			$HR_{relapse}=1$ $HR_{death\_without\_relapse}=0.5$ $HR_{death\_after\_relapse}=0.5$			$HR_{relapse}=0.5$ $HR_{death\_without\_relapse}=1$ $HR_{death\_after\_relapse}=0.5$		
θ		**BIAS**	**MSE**	**CP(%)**	**BIAS**	**MSE**	**CP(%)**	**BIAS**	**MSE**	**CP(%)**	**BIAS**	**MSE**	**CP(%)**
0.5	θ	-0.056	0.233	95.3	-0.049	0.203	97.0	-0.034	0.181	95.8	-0.058	0.241	95.8
	β_1	0.000	0.036	94.8	0.001	0.037	95.0	-0.001	0.035	94.5	-0.010	0.042	94.8
	β_2	-0.002	0.104	95.3	0.009	0.087	95.6	-0.020	0.120	95.8	-0.003	0.087	94.9
	β_3	0.003	0.061	94.8	-0.009	0.070	95.0	-0.010	0.058	95.4	-0.015	0.080	95.7
	λ_1	0.005	0.029	95.7	0.004	0.027	95.4	0.007	0.027	95.2	0.006	0.029	95.6
	λ_2	0.001	0.028	95.0	0.000	0.026	95.0	0.004	0.024	95.0	0.002	0.028	95.6
	λ_3	0.013	0.034	95.2	0.012	0.033	95.1	0.013	0.031	95.0	0.015	0.034	95.2
	γ_1	0.013	0.008	95.3	0.012	0.008	95.0	0.012	0.007	96.1	0.013	0.008	95.6
	γ_2	0.044	0.057	96.1	0.037	0.046	96.1	0.048	0.056	95.3	0.041	0.048	95.8
	γ_3	0.020	0.026	95.3	0.021	0.025	95.5	0.018	0.021	95.7	0.023	0.030	95.1
1	θ	-0.001	0.094	94.0	-0.002	0.081	94.8	0.007	0.073	93.8	-0.005	0.099	94.4
	β_1	0.012	0.045	94.6	0.012	0.046	94.9	0.014	0.043	95.5	0.000	0.052	95.1
	β_2	0.000	0.117	94.9	0.015	0.104	96.3	-0.016	0.138	95.1	-0.005	0.100	95.1
	β_3	0.017	0.070	95.9	0.011	0.085	95.9	0.004	0.071	95.4	0.001	0.102	94.1
	λ_1	0.003	0.042	95.1	0.001	0.040	95.6	0.003	0.038	94.8	0.002	0.044	94.9
	λ_2	0.006	0.033	94.9	0.005	0.030	95.2	0.007	0.028	94.6	0.007	0.032	95.1
	λ_3	0.001	0.034	96.0	0.000	0.034	95.6	-0.001	0.032	96.1	0.004	0.035	95.7
	γ_1	0.019	0.010	94.3	0.017	0.010	94.9	0.019	0.009	95.5	0.019	0.011	94.1
	γ_2	0.047	0.057	95.3	0.043	0.049	95.4	0.046	0.055	94.6	0.044	0.053	94.9
	γ_3	0.024	0.025	94.7	0.026	0.028	95.1	0.023	0.023	95.0	0.028	0.032	94.7
2	θ	0.020	0.044	94.6	0.025	0.046	94.2	0.017	0.044	94.2	0.024	0.055	94.0
	β_1	0.009	0.072	94.6	0.011	0.074	94.5	0.008	0.070	94.9	-0.009	0.079	94.7
	β_2	-0.014	0.148	94.5	0.006	0.152	94.7	-0.024	0.169	94.3	-0.015	0.142	95.5
	β_3	-0.003	0.098	93.2	-0.015	0.111	94.4	-0.012	0.099	93.9	-0.027	0.127	93.7
	λ_1	0.017	0.060	95.5	0.022	0.061	95.1	0.015	0.060	94.9	0.022	0.065	94.8
	λ_2	0.019	0.035	94.5	0.023	0.037	94.0	0.017	0.035	94.7	0.022	0.040	94.5
	λ_3	0.013	0.043	95.4	0.015	0.043	95.4	0.013	0.043	95.4	0.017	0.044	95.6
	γ_1	0.024	0.011	94.3	0.027	0.012	94.9	0.022	0.011	94.2	0.028	0.013	94.9
	γ_2	0.055	0.046	95.6	0.062	0.050	95.4	0.055	0.049	95.4	0.061	0.054	95.0
	γ_3	0.025	0.020	94.8	0.028	0.023	94.7	0.024	0.019	94.8	0.032	0.027	95.2

Restrictive Compartment Model:

Tables 7 to 10 present simulation results based on the Restrictive model obtained via the NR algorithm, varying the effects of treatment on relapse ($HR_{relapse}$ = 0.5, 1) and on death (HR_{death} = 0.5, 1, 2).

When there is no treatment effect, that is $HR_{relapse} = HR_{death} = 1$, considering the simulation setting of n = 200 with 30% censoring, biases in the estimates are relatively close to zero as compared to the true parameter values with coverage probabilities approaching 95% for all degrees of dependence (θ) (Table 7). The effect of treatment does not appear to have any influence on the magnitudes of the biases and MSEs of the parameter estimates.

Similar to the General model, comparatively larger MSEs for θ, as compared to the other parameters, are observed when θ = 0.5. However, the MSE decreases as θ increases. The CPs of all parameters are close to the nominal level of 95% for all values of θ considered. In addition, the MSEs for β_1 and β_2 generally increase when θ increases.

Table 7: Simulation results obtained from the Restrictive compartment model varying θ, exp(β_1) and exp(β_2), λ_1 = 2, λ_2= 1, λ_3 = 1, γ_1 = 1, γ_2 = 2, γ_3 = 1 for n = 200 with 30% censoring.

		$HR_{relapse}$ = 1 HR_{death} = 1			$HR_{relapse}$ = 1 $HR_{death\_}$ = 2			$HR_{relapse}$ = 1 $HR_{death\_}$ = 0.5			$HR_{relapse}$ = 0.5 $HR_{death\_}$ = 0.5		
θ		**BIAS**	**MSE**	**CP(%)**	**BIAS**	**MSE**	**CP(%)**	**BIAS**	**MSE**	**CP(%)**	**BIAS**	**MSE**	**CP(%)**
0.5	θ	-0.030	0.085	96.0	-0.028	0.087	97.3	-0.028	0.075	96.5	-0.031	0.087	96.3
	β_1	-0.010	0.049	94.3	-0.010	0.052	95.3	-0.011	0.050	94.9	-0.018	0.054	94.9
	β_2	-0.006	0.051	94.6	0.004	0.052	95.0	0.004	0.048	94.7	-0.016	0.054	94.0
	λ_1	0.012	0.029	94.4	0.011	0.030	95.1	0.010	0.028	94.6	0.011	0.029	94.6
	λ_2	0.000	0.007	94.3	0.001	0.008	94.3	0.000	0.007	94.3	0.000	0.007	94.3
	γ_1	0.012	0.007	95.4	0.011	0.007	95.3	0.010	0.007	94.9	0.011	0.007	95.2
	γ_2	0.026	0.024	94.9	0.026	0.024	95.1	0.023	0.022	94.4	0.026	0.024	94.9
1	θ	-0.004	0.042	94.9	-0.001	0.044	95.3	-0.004	0.041	95.2	-0.005	0.044	94.8
	β_1	0.001	0.062	95.6	0.000	0.064	95.5	-0.001	0.063	95.9	-0.010	0.066	95.9
	β_2	-0.010	0.063	95.0	-0.004	0.069	94.7	0.000	0.065	94.9	-0.014	0.066	95.0
	λ_1	0.006	0.039	94.9	0.007	0.039	95.1	0.006	0.038	94.6	0.006	0.038	94.5
	λ_2	0.009	0.009	95.4	0.010	0.009	95.0	0.008	0.009	94.7	0.008	0.009	94.6
	γ_1	0.014	0.008	94.0	0.014	0.009	93.5	0.013	0.008	93.7	0.014	0.009	93.3
	γ_2	0.020	0.026	94.9	0.021	0.026	94.2	0.020	0.025	94.6	0.020	0.026	94.4
2	θ	0.006	0.026	95.2	0.005	0.026	95.0	0.003	0.025	94.4	0.004	0.027	94.4
	β_1	0.007	0.096	94.8	0.006	0.101	94.6	0.004	0.098	95.0	-0.008	0.104	94.0
	β_2	-0.001	0.096	95.7	0.009	0.098	95.5	0.008	0.097	95.5	-0.013	0.098	96.3
	λ_1	0.002	0.062	93.7	0.002	0.062	93.1	0.001	0.061	93.5	0.002	0.061	93.6
	λ_2	0.004	0.014	94.8	0.004	0.014	94.9	0.003	0.014	94.9	0.004	0.014	95.1
	γ_1	0.017	0.008	94.2	0.017	0.009	93.6	0.016	0.009	93.9	0.017	0.009	94.0
	γ_2	0.034	0.026	94.3	0.034	0.026	94.5	0.032	0.024	94.8	0.034	0.026	95.2

The conclusions drawn with regards to the biases and MSEs of θ, β_1 and β_2 remained similar to those obtained under the General model setting, when the proportion of censoring increased from 30% to 50% (Table 8). Under weak dependence, a comparatively larger MSE of θ in relation to the other parameters, ranging from 0.087 to 0.165, was observed. However, the CP was rather conservative. A decreasing MSE for θ is observed as θ increases.

Table 8: Simulation results obtained from the Restrictive compartment model varying θ, exp(β_1) and exp(β_2), λ_1 = 2, λ_2 = 1, λ_3 = 1, γ_1 = 1, γ_2 = 2, γ_3 = 1 for n = 200 with 50% censoring.

		$HR_{relapse}$ = 1 HR_{death} = 1			$HR_{relapse}$ = 1 $HR_{death\_}$ = 2			$HR_{relapse}$ = 1 $HR_{death\_}$ = 0.5			$HR_{relapse}$ = 0.5 $HR_{death\_}$ = 0.5		
θ		**BIAS**	**MSE**	**CP(%)**	**BIAS**	**MSE**	**CP(%)**	**BIAS**	**MSE**	**CP(%)**	**BIAS**	**MSE**	**CP(%)**
0.5	θ	-0.040	0.130	95.2	-0.049	0.165	95.2	-0.029	0.102	96.1	-0.031	0.087	96.3
	β_1	-0.011	0.052	94.6	-0.011	0.057	95.1	-0.010	0.054	95.1	-0.018	0.054	94.9
	β_2	-0.010	0.059	94.7	0.002	0.065	94.4	0.003	0.056	94.9	-0.016	0.054	94.0
	λ_1	0.014	0.031	94.6	0.012	0.034	95.3	0.012	0.031	95.1	0.011	0.029	94.6
	λ_2	0.000	0.009	93.5	-0.001	0.011	94.6	0.001	0.009	94.4	0.000	0.007	94.3
	γ_1	0.014	0.008	96.0	0.014	0.008	95.8	0.013	0.008	95.1	0.011	0.007	95.2
	γ_2	0.029	0.029	95.3	0.028	0.031	96.1	0.029	0.027	95.6	0.026	0.024	94.9
1	θ	-0.011	0.065	94.7	-0.012	0.066	94.9	-0.008	0.052	95.1	-0.005	0.044	94.8
	β_1	-0.002	0.066	95.8	-0.001	0.070	95.9	-0.001	0.066	96.1	-0.010	0.066	95.9
	β_2	-0.014	0.072	95.6	-0.002	0.077	95.7	-0.002	0.071	95.5	-0.014	0.066	95.0
	λ_1	0.007	0.044	94.7	0.005	0.045	94.5	0.005	0.041	95.2	0.006	0.038	94.5
	λ_2	0.010	0.010	95.7	0.009	0.011	95.6	0.008	0.010	95.5	0.008	0.009	94.6
	γ_1	0.015	0.009	94.4	0.014	0.010	95.4	0.013	0.009	94.1	0.014	0.009	93.3
	γ_2	0.025	0.033	94.1	0.025	0.034	94.2	0.021	0.029	94.9	0.020	0.026	94.4
2	θ	0.010	0.035	95.9	0.009	0.038	94.8	0.006	0.031	95.3	0.004	0.027	94.4
	β_1	0.006	0.101	95.3	0.004	0.108	95.1	0.003	0.105	94.4	-0.008	0.104	94.0
	β_2	0.001	0.108	96.0	0.016	0.114	95.6	0.011	0.106	95.7	-0.013	0.098	96.3
	λ_1	0.008	0.067	94.2	0.006	0.069	93.1	0.005	0.065	93.7	0.002	0.061	93.6
	λ_2	0.006	0.016	94.7	0.004	0.017	94.9	0.004	0.015	94.6	0.004	0.014	95.1
	γ_1	0.021	0.010	93.5	0.020	0.011	94.2	0.019	0.010	94.6	0.017	0.009	94.0
	γ_2	0.041	0.035	95.2	0.040	0.036	94.9	0.037	0.030	94.8	0.034	0.026	95.2

Increasing the sample size from $n = 200$ to $n = 300$ improves the precision of the parameter estimates. In general, biases for all estimates are even closer to zero with the increase in sample size. Additionally, a notable decrease in MSEs of the estimates are observed. The 95% coverage probability is also reached for almost all estimates (Tables 9 and 10).

Table 9: Simulation results obtained from the Restrictive compartment model varying θ, exp(β_1) and exp(β_2), λ_1 = 2, λ_2 = 1, λ_3 = 1, γ_1 = 1, γ_2 = 2, γ_3 = 1 for n = 300 with 30% censoring.

		$HR_{relapse}$ = 1 HR_{death} = 1			$HR_{relapse}$ = 1 $HR_{death\_}$ = 2			$HR_{relapse}$ = 1 $HR_{death\_}$ = 0.5			$HR_{relapse}$ = 0.5 $HR_{death\_}$ = 0.5		
θ		**BIAS**	**MSE**	**CP(%)**	**BIAS**	**MSE**	**CP(%)**	**BIAS**	**MSE**	**CP(%)**	**BIAS**	**MSE**	**CP(%)**
0.5	θ	-0.017	0.057	95.1	-0.020	0.062	96.1	-0.019	0.052	95.7	-0.023	0.061	96.1
	β_1	0.010	0.032	95.0	0.012	0.034	95.3	0.012	0.032	95.3	0.009	0.035	94.9
	β_2	0.004	0.035	93.3	0.007	0.037	94.3	0.008	0.034	94.2	0.000	0.036	93.9
	λ_1	-0.005	0.019	94.8	-0.004	0.019	94.9	-0.005	0.018	94.5	-0.006	0.019	95.0
	λ_2	0.000	0.005	94.8	0.001	0.005	94.5	0.000	0.004	95.1	0.000	0.004	95.1
	γ_1	0.005	0.005	93.6	0.006	0.005	95.1	0.005	0.005	95.0	0.006	0.005	95.2
	γ_2	0.013	0.015	95.7	0.013	0.016	94.8	0.012	0.014	96.3	0.010	0.015	95.7
1	θ	-0.006	0.028	95.6	-0.007	0.029	94.6	-0.008	0.026	95.1	-0.006	0.030	95.7
	β_1	-0.008	0.045	94.6	-0.010	0.046	95.1	-0.009	0.045	94.8	-0.013	0.047	94.9
	β_2	-0.013	0.043	95.2	-0.004	0.044	95.5	-0.003	0.043	95.3	-0.018	0.044	95.2
	λ_1	0.005	0.024	95.8	0.004	0.024	96.0	0.004	0.024	95.5	0.005	0.024	95.4
	λ_2	0.003	0.006	95.0	0.002	0.006	94.5	0.002	0.006	94.7	0.003	0.006	94.6
	γ_1	0.006	0.004	96.2	0.005	0.004	96.4	0.006	0.004	96.3	0.006	0.004	96.9
	γ_2	0.018	0.015	95.7	0.019	0.015	95.8	0.018	0.014	96.6	0.018	0.015	95.7
2	θ	0.006	0.016	95.5	0.006	0.016	96.1	0.007	0.015	96.1	0.006	0.016	95.0
	β_1	-0.011	0.067	95.1	-0.015	0.070	94.9	-0.013	0.069	95.1	-0.021	0.072	95.0
	β_2	-0.006	0.067	94.9	0.002	0.070	94.4	0.000	0.069	94.5	-0.015	0.067	95.3
	λ_1	0.009	0.040	93.8	0.009	0.040	94.2	0.007	0.039	94.1	0.007	0.040	94.3
	λ_2	0.004	0.009	95.5	0.003	0.009	95.4	0.003	0.009	95.4	0.003	0.009	95.5
	γ_1	0.011	0.005	95.9	0.010	0.005	96.0	0.009	0.005	95.7	0.009	0.005	95.9
	γ_2	0.023	0.015	95.3	0.023	0.016	94.5	0.022	0.015	95.4	0.023	0.016	95.7

Table 10: Simulation results obtained from the Restrictive compartment model varying θ, exp(β_1) and exp(β_2), λ_1 = 2, λ_2 = 1, λ_3 = 1, γ_1 = 1, γ_2 = 2, γ_3 = 1 for n = 300 with 50% censoring.

		$HR_{relapse}$ = 1 HR_{death} = 1			$HR_{relapse}$ = 1 $HR_{death\_}$ = 2			$HR_{relapse}$ = 1 $HR_{death\_}$ = 0.5			$HR_{relapse}$ = 0.5 $HR_{death\_}$ = 0.5		
θ		**BIAS**	**MSE**	**CP(%)**	**BIAS**	**MSE**	**CP(%)**	**BIAS**	**MSE**	**CP(%)**	**BIAS**	**MSE**	**CP(%)**
0.5	θ	-0.024	0.081	96.3	-0.029	0.103	95.6	-0.024	0.072	96.0	-0.029	0.099	95.6
	β_1	0.012	0.034	95.0	0.013	0.037	93.8	0.012	0.035	94.6	0.008	0.039	95.1
	β_2	0.000	0.041	93.7	0.008	0.044	94.5	0.005	0.039	94.6	-0.005	0.046	93.5
	λ_1	-0.004	0.020	95.3	-0.003	0.022	95.9	-0.004	0.020	95.5	-0.003	0.021	95.1
	λ_2	0.002	0.006	93.9	0.001	0.007	94.5	0.002	0.005	94.3	0.002	0.006	93.8
	γ_1	0.007	0.006	94.7	0.008	0.006	94.3	0.006	0.005	95.6	0.007	0.006	94.5
	γ_2	0.015	0.018	94.9	0.015	0.020	94.8	0.014	0.017	95.3	0.015	0.020	94.7
1	θ	-0.004	0.044	94.4	-0.006	0.045	94.6	-0.004	0.035	95.5	-0.005	0.047	94.5
	β_1	-0.009	0.048	94.9	-0.009	0.049	95.4	-0.009	0.047	94.7	-0.015	0.052	94.8
	β_2	-0.009	0.050	95.2	-0.002	0.050	96.6	-0.002	0.046	95.7	-0.016	0.052	95.3
	λ_1	0.007	0.028	95.6	0.005	0.028	95.6	0.005	0.026	95.4	0.006	0.028	95.7
	λ_2	0.003	0.007	94.4	0.002	0.008	94.7	0.002	0.007	94.4	0.002	0.007	94.6
	γ_1	0.008	0.005	95.6	0.007	0.005	95.3	0.007	0.005	95.6	0.008	0.005	96.7
	γ_2	0.023	0.020	94.9	0.022	0.020	95.4	0.019	0.017	95.9	0.022	0.020	94.9
2	θ	0.005	0.024	95.4	0.005	0.024	95.9	0.004	0.020	96.0	0.005	0.024	95.6
	β_1	-0.015	0.069	95.3	-0.020	0.073	94.8	-0.016	0.071	94.7	-0.025	0.074	95.5
	β_2	-0.007	0.076	94.8	0.000	0.080	94.5	0.003	0.074	93.8	-0.016	0.076	95.6
	λ_1	0.011	0.044	93.5	0.011	0.045	94.6	0.008	0.042	94.4	0.008	0.043	95.0
	λ_2	0.002	0.011	95.8	0.002	0.011	95.6	0.001	0.010	95.6	0.002	0.010	95.3
	γ_1	0.013	0.006	95.2	0.012	0.006	96.1	0.010	0.005	96.3	0.010	0.006	96.1
	γ_2	0.024	0.021	95.3	0.022	0.022	95.1	0.021	0.018	95.8	0.022	0.021	95.1

Similar to the General model, while the MSE of θ is relatively large under weak dependence, it decreases when θ increases. In addition, the MSEs of the estimates for treatment effects increase as θ increases. Nonetheless, the magnitudes of the MSE in the restrictive model are by and large smaller than those observed in the General model. Coverage probabilities of 95% are reached for all parameters in the Restrictive model on the whole. In the Restrictive model, an increase in the biases and MSEs of θ is observed when the proportion of censoring of death increases from 30% to 50%, regardless of the magnitude of treatment effect. However, the increase in the proportion of censored observations seemed to have little effect on the biases and MSEs of the other parameters. As the proportion of censored observations increase, a corresponding increase in the magnitude of biases and MSEs of the other parameters was also experienced. An increase in sample size also decreases the magnitude of the biases and MSEs of all parameters, which is similar to the conclusions drawn if the General model was used.

To summarize, estimates of the degree of dependence between relapse and death are subjected to a greater bias and MSE if the underlying dependence is weak. Estimates of the treatment effects are probably less precise if the degree of dependence is at least moderate. It was noted that as θ increases, the variances of the covariates, in particular, increase. CPs are generally close to the nominal level of 95% for all simulation settings based on the Restrictive and General model. MSEs of small to moderate magnitudes are also observed for the parameters.

Hence, our simulation studies suggest that parameters estimated via our proposed method are relatively unbiased with small to moderate variances, depending on the degree of dependence.

Chapter 5: Application to the nasopharyngeal cancer clinical trial dataset

The incidence of nasopharyngeal cancer (NPC) among males hovered at a numerical value of 14 per 100,000 person-years in the period from 1968-1972 to 1993-1997, until it showed a decline in 1998-2002. A similar trend was observed among females where the incidence remained at about 6.0 per 100,000 person-years from 1968-1972 to 1993-1997, before decreasing to 3.7 per 100,000 person-years in 1998-2002. Despite showing a decline, NPC is by far one of the most frequently occurring cancers among Singaporeans, and one of the most common causes of death among cancer patients[39]. Hence, there is a need to explore treatment regimes for NPC.

Radiotherapy (RT) is expected to cure about 50% of patients inflicted with NPC. It is estimated that about 30% of patients will develop loco-regional recurrence after a full course of RT, and half of the patients with very large and/or supraclavicular lymph nodes will relapse distantly.[40] Chemotherapy has been used to treat metastatic or recurrent NPC, with overall response rates of 50-80% with the use of platinum based combinations. In the adjuvant setting, however, the results have been controversial.

Therefore, a randomized clinical trial on NPC was conducted in Singapore to assess the therapeutic intervention of standard RT versus concurrent chemo-radiotherapy followed by adjuvant chemotherapy.[4] Eligible patients who were diagnosed with stage III or IV (non-metastatic) NPC were recruited between September 1997 and May 2003 following informed consent. Patients who had previous treatment for NPC, signs of distant metastasis, and other concomitant malignant disease were excluded from the trial. A total of 221 patients were randomly assigned to receive only radiotherapy (RT; n = 110) or concurrent chemo-radiotherapy followed by adjuvant chemotherapy (CRT; n = 111). For patients on CRT, they were treated with concurrent cisplatin (CDDP) and RT before proceeding on to adjuvant CDDP and fluorouracil (FU). Dose schedules for patients on CRT are presented in Table 11. All patients were required to be followed up every 4 months for the first year, every 6 months for the second and third year and every year thereafter. The median follow-up time was reported to be 3.2 years. Full details of the trial are provided by Wee *et al.*[4]

Table 11: Dose schedules for patients on the CRT arm[4]

Therapy	Dose	Route	Week	Day
Concurrent chemoradiotherapy				
CDDP	1.) 25 mg/m^2/d for 4 days	IV over 6-8 hrs	1	1-4
			4	22-25
			7	43-46
	2.) Alternatively, 30/30/40 mg/m^2/d for 3 days if patient starts RT on a Wednesday and only for the first cycle		1	1-3
			4	22-25
			7	43-46
RT	2 Gy/d			35 daily fractions
	5 fractions/wk			
Adjuvant chemotherapy				
CDDP	20 mg/m^2/d for 4 days	IV over 6-8 hrs	11	71-74
			15	99-102
			19	127-130
FU	1,000 mg/m^2/d for 4 days	IV over 6-8 hrs	11	71-74
			15	99-102
			19	127-130

Abbreviations: CDDP, cisplatin; RT, radiotherapy; IV, intravenous; FU, fluorouracil.

Typically, patients with NPC will undergo RT and/or CRT treatment, and then enjoy a disease-free period. During the course of treatment, they may develop a distant metastasis (disease-spread usually at the lung or the bone) or a local recurrence. It is also possible that the patient may even die before any of these events has occurred, for example from pneumonia or a treatment related cause such as neutropenic sepsis.

In this trial, two endpoints were of interest – time to relapse and time to mortality. Although death was the primary outcome, relapse was also considered to be an important endpoint because it has been found that a substantial proportion of patients with Stage III or IV endemic NPC relapsed locoregionally and/or systematically with RT alone.

Altogether, there were 75 relapses. Of these, 20 patients remained alive without any evidence of disease and 55 died following a relapse. In addition, there were 13 deaths without a prior relapse being reported. Table 12 gives a breakdown of the events which have occurred in each treatment group.

Table 12: Breakdown of events in the CRT and RT groups

Type of event occurred	CRT	RT	Total
Relapse, and then death	16	39	55
Death without relapse	8	5	13
Relapse without death	11	9	20

With a substantial number of deaths following relapse, it is anticipated that death (terminal event) may be strongly related to relapse (non-terminal event). As a consequence, a semi-competing risks approach, which is intended to account for the correlation between relapse and death, will be appropriate for analyzing such data following a natural order of disease progression. Our proposed methodology was thus applied to the NPC data, by modeling the dependence between the relapse and death times via the frailty approach.

Parameter estimates describing the relationship for relapse and death in the NPC dataset for the General Compartment model are presented in Table 13. A positive dependence structure was observed between relapse and death times, with an association parameter of 6.79 (95% CI: 3.70, 12.46). This indicates that relapse is highly associated with death. After accounting for the dependence between relapse and death, patients on CRT were observed to be at a lower risk of death after relapse than those on RT, with a HR = exp(β_3) of 0.47 although this was not significant (95% CI: 0.15, 1.48). Among patients without relapse, patients on CRT were observed to be at a slightly higher risk of death than those on RT with a HR = exp(β_2) of 1.26, but this difference was not significant (95% CI: 0.31, 5.10). The HR of relapse comparing patients on CRT and those on RT = exp(β_1) is 0.44 (95% CI: 0.16, 1.20). The shape parameters were also observed to be greater than 1, and were statistically significant. This suggests that the risk of a relapse or death increased over time. The risk of death increased, regardless of whether there was a previous occurrence of relapse.

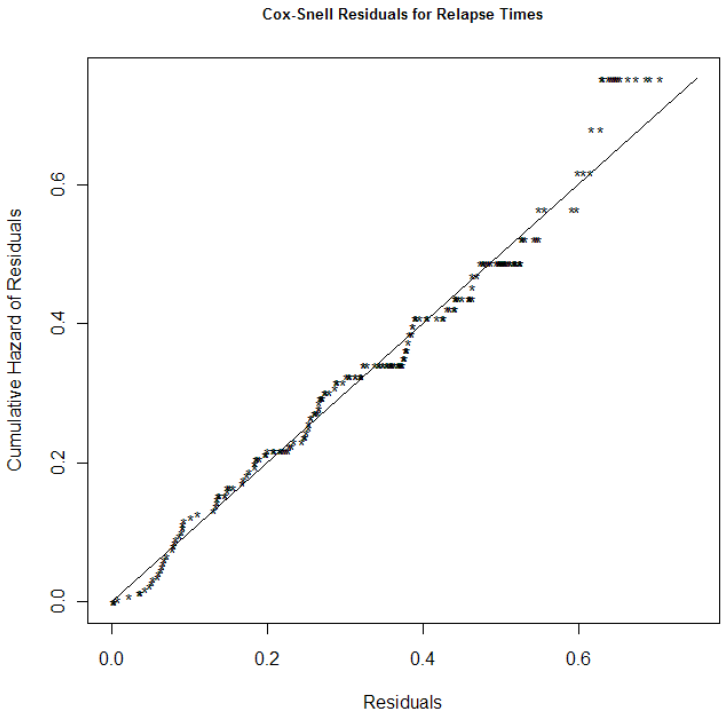
Table 13: Parameter estimates based on the proposed General Compartment model (data from NPC trial by Wee *et al.*[4])

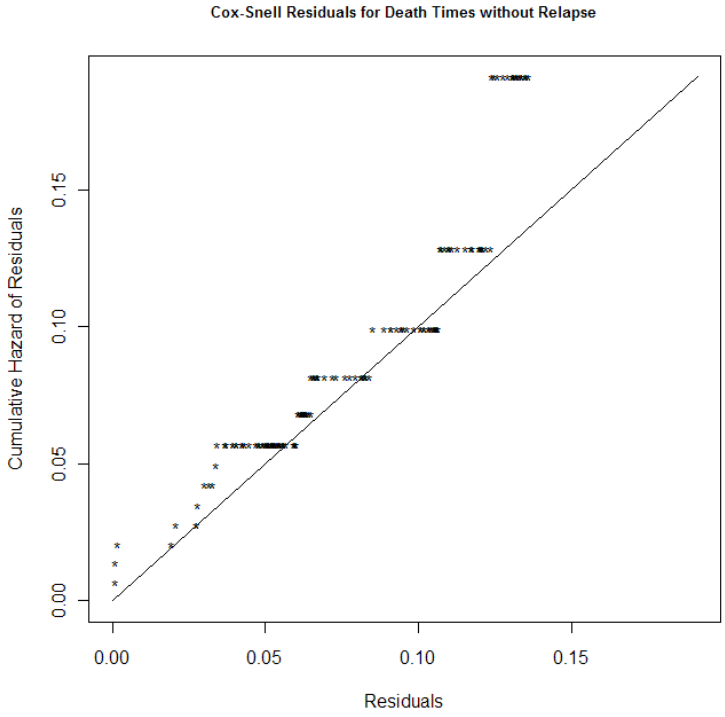
Parameters	Estimate	95% CI	exp(Estimate) (95% CI)
θ'	1.92	(1.31, 2.52)	6.79 (3.70, 12.46)
β_1	-0.82	(-1.82, 0.18)	0.44 (0.16, 1.20)†
β_2	0.23	(-1.18, 1.63)	1.26 (0.31, 5.10)†
β_3	-0.75	(-1.89, 0.39)	0.47 (0.15, 1.48)†
λ_1'	-0.24	(-0.77, 0.29)	0.79 (0.47, 1.34)
λ_2'	-1.44	(-2.60, -0.28)	0.24 (0.07, 0.75)
λ_3'	-0.72	(-1.04, -0.40)	0.49 (0.35, 0.67)
γ_1'	0.74	(0.42, 1.06)	2.10 (1.53, 2.89)
γ_2'	0.61	(0.16, 1.06)	1.84 (1.17, 2.90)
γ_3'	0.97	(0.64, 1.30)	2.64 (1.91, 3.68)

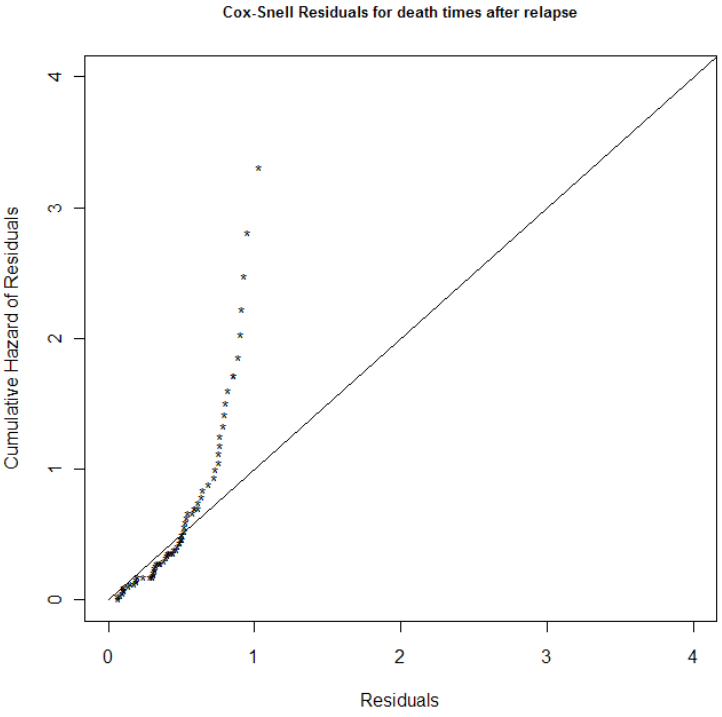
†: Corresponds to hazards ratio (HR)

The adequacy of our model was checked via Cox-Snell residuals. The following figures show the residuals for the event times in each of the 3 paths of the general compartment model.

Figure 6: Cox-Snell residuals for time to relapse, times to death without prior relapse, and following relapse based on the general compartment model using data from NPC trial by Wee *et al.*[4]




Cox-Snell Residuals for Death Times without Relapse
Cumulative Hazard of Residuals
0.00
0.05
0.10
0.15
Residuals


Cox-Snell Residuals for death times after relapse
Cumulative Hazard of Residuals
0
1
2
3
4
Residuals

It was observed that the residuals for the path to relapse in the General compartment model generally lie closely on the line of identity, indicating an adequate model fit. However, there appears to be a slight deviation from the line of identity in the Cox-Snell residuals at the tail-end distribution of death times without relapse. The deviation is most likely to be contributed by individuals who were followed for a much longer period of time exceeding 5 years, without experiencing any relapse or death. In the same plot, we also noticed a "step-like" function. The study sample involved in this second plot are patients who were uncensored on both events (n = 133) and those who experienced only death (n = 13). Hence, the "steps" are likely due to the substantial proportion of subjects being censored on both events – relapse and death. It was also noted that small residuals of magnitude very much less than 3 were observed for relapse and death without relapse. This could be due to the high probability of relapse and death without relapse. There were 75 relapses out of 220 patients, with 48 and 27 relapses in RT and CRT groups respectively. When recurrence-free survival was considered, median time to relapse was reached at 4.1 years for the RT group. Patients on the CRT arm did not reach median relapse-free survival. Among patients who did not experience any relapse, median survival was not reached in any of the RT or CRT groups. A lack of fit was also observed for the path from relapse to death, since residuals did not fall near to the line of identity. The lack of fit could have come about when we constrained the shapes and scales for the baseline hazards for each treatment group to be the same for each compartment arm. When a sub-group analysis was performed for each RT and CRT group, a

difference in the shape parameters for relapse to death arm comparing between RT and CRT was observed. While a shape parameter of 3.75 (95% CI: 2.65, 5.30) was observed in the RT group, a shape parameter of 1.04 (95% CI: 0.32, 3.41) was observed in the CRT group. As the shape parameters are statistically greater than 1 among the patients on CRT and RT, it suggests that the risk of relapse and death both increase over time among these 2 groups of patients. Results are presented in Tables 14 and 15.

Table 14: Parameter estimates based on the proposed General Compartment model for patients under radiotherapy (data from NPC trial by Wee *et al.*[4])

Parameters	Estimate	95% CI	exp(Estimate) (95% CI)
θ'	1.86	(1.16, 2.56)	6.42 (3.19, 12.95)
λ_1'	-0.13	(-0.66, 0.41)	0.88 (0.52, 1.51)
λ_2'	-1.19	(-2.31, -0.07)	0.30 (0.10, 0.94)
λ_3'	-0.71	(-0.97, -0.44)	0.49 (0.38, 0.64)
γ_1'	0.84	(0.45, 1.24)	2.32 (1.56, 3.45)
γ_2'	0.72	(0.12, 1.33)	2.06 (1.12, 3.79)
γ_3'	1.32	(0.98, 1.67)	3.75 (2.65, 5.30)

Table 15: Parameter estimates based on the proposed General Compartment model for patients under chemo-radiotherapy (data from NPC trial by Wee *et al.*[4])

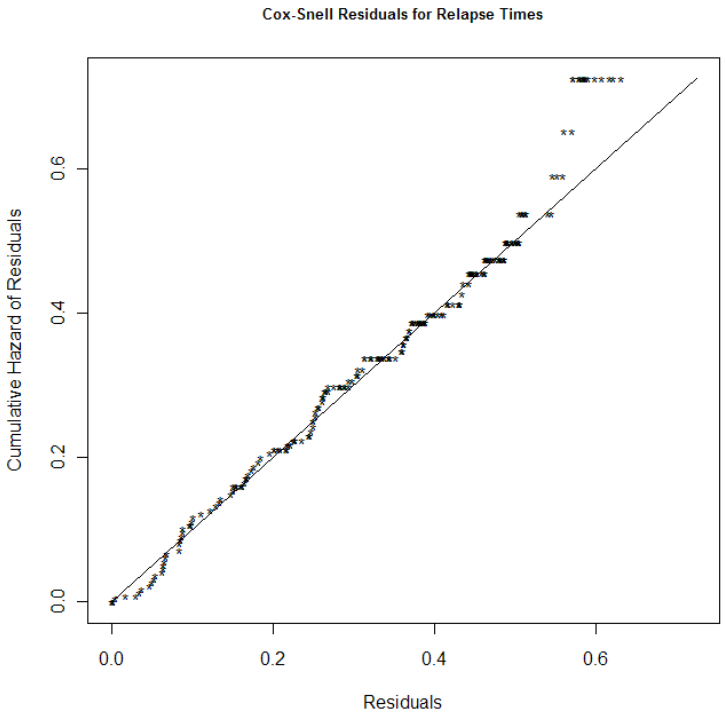
Parameters	Estimate	95% CI	exp(Estimate) (95% CI)
θ'	2.28	(1.50, 3.06)	9.77 (4.46, 21.37)
λ_1'	-0.53	(-1.22, 0.15)	0.59 (0.30, 1.16)
λ_2'	-1.18	(-2.30, -0.06)	0.31 (0.10, 0.94)
λ_3'	-1.05	(-1.93, -0.17)	0.35 (0.15, 0.84)
γ_1'	0.80	(0.29, 1.31)	2.23 (1.33, 3.71)
γ_2'	0.67	(0.04, 1.30)	1.95 (1.04, 3.66)
γ_3'	0.04	(-1.15, 1.23)	1.04 (0.32, 3.41)

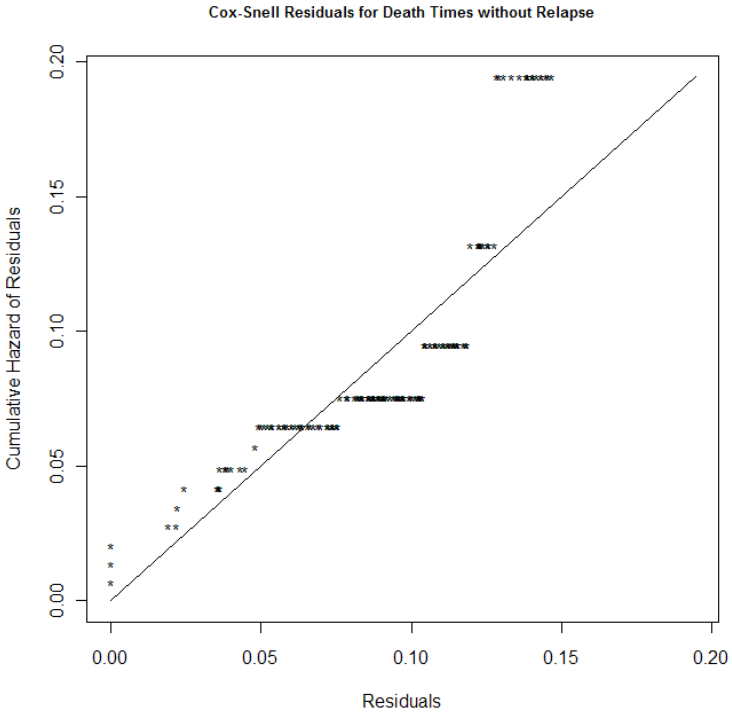
We further attempted to demonstrate that the scale parameter is similar between CRT and RT, while the shape parameter differs between the 2 treatment

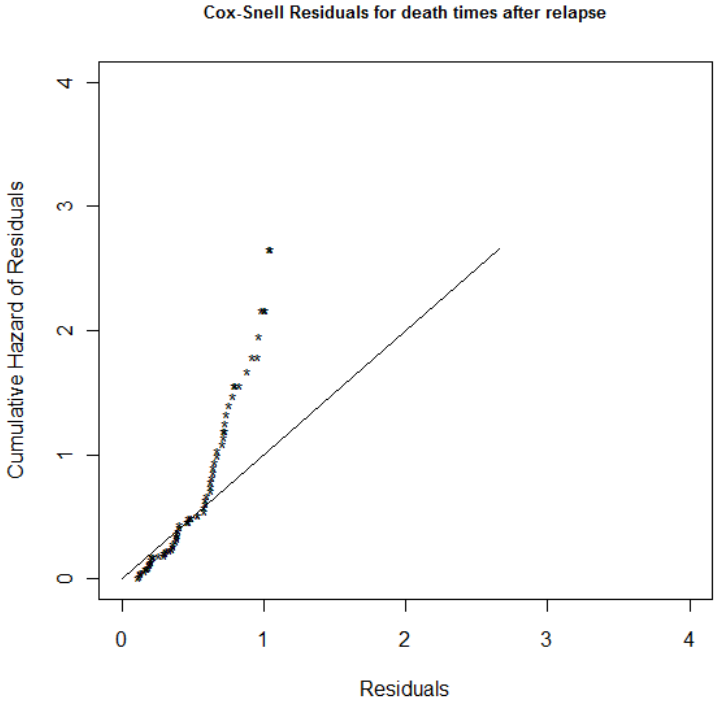
groups via another alternative method. In this alternative method, we estimated the treatment effect on the scale and shape parameters via β_3 and β_3^* in $\lambda'(X) = e^{\lambda' + \beta_3 X}$ and $\gamma'(X) = \gamma' e^{\beta_3^* X}$ respectively. From these 2 equations, we allowed the scale and shape parameters to vary with the covariate *x*, where *x* is the treatment covariate (given by CRT coded as 1; RT coded as 0) in this study. While the magnitude of the scale is similar between CRT and RT (β_3 = -1.05 – (-0.71) = -0.34; 95% CI: -0.26, 0.57), the shape parameter differs between the 2 treatment groups (β_3^* = log(1.04) - log(3.75) = -1.28; 95% CI: -2.52, -0.04). Hence, this suggests that the shape parameter for CRT is exp(-1.28) = 0.28 times that for RT in the relapse to death pathway in the compartment model, which corresponds to what we have observed in Tables 14 and 15.

A special case of the General Model, which imposes more restrictive assumptions of β_2 = β_3 and $h_{02} = h_{03}$, was also considered. A likelihood ratio test comparing β_2 = β_3, as well as parameters relating to the hazards namely γ_2 = γ_3 and λ_2 = λ_3 simultaneously using the chi-square test statistic with 3 degrees of freedom as described in Section 3.3.2, shows that equality holds for all 3 sets of parameters ($\chi^2_{(3)}$ = 0.922; p = 0.82). Hence, it suggests that a reduced Restrictive model is sufficient for describing the data. The adequacy of the restrictive model was also checked via the Cox-Snell residuals in Figure 7. A lack of fit was also observed for the patients who died, regardless of whether they experienced a relapse. However, the inadequacy of model fit was more apparent in the relapse to death path of the compartment model.

Figure 7: Cox-Snell residuals for time to relapse and to death based on the restrictive compartment model using data from NPC trial by Wee *et al.*[4]




Cox-Snell Residuals for Death Times without Relapse
Cumulative Hazard of Residuals
0.00
0.05
0.10
0.15
0.20
Residuals


Cox-Snell Residuals for death times after relapse
Cumulative Hazard of Residuals
0
1
2
3
4
Residuals

Under this Restrictive Model, it is shown that patients on CRT have a lower risk of death as compared to those on RT, regardless of whether they had a prior relapse (HR = exp(β_2) = 0.59; 95% CI: 0.19, 1.82). In addition, patients on CRT have a lower risk of relapse as compared to those on RT (HR = exp(β_1) = 0.42; 95% CI: 0.14, 1.27). The amount of relatedness between relapse and death was quantified by an association parameter of 8.96 (95% CI: 6.31, 12.72) (Table 16).

When both the General and Restrictive models were implemented, the HR of relapse comparing CRT and RT patients were similar (HR of 0.44 based on the General model versus 0.42 based on the Restrictive model). The HR of death could not be directly compared between the two models, as we have allowed the hazards of death to vary after relapse for the General model. While the Restrictive model may be valid for the data from the likelihood ratio test, the General model probably provided more information on the hazards of death on the disease process in the NPC data. It was observed that treatment seemed to have a different impact on the risk of death among patients who have suffered a relapse, and those who had not. While it was observed that patients on CRT had a higher risk of death before relapse than those on RT alone (HR = 1.26; 95% CI: 0.31, 5.10), a protective effect was observed among patients who had relapsed (HR = 0.47, 95% CI: 0.15, 1.48). However, it should be noted that the elevated risk of death without relapse should be interpreted with caution, as there were only 13 deaths without relapse out of 220 patients. The Restrictive model showed that CRT

lowered the risk of death as compared to RT in general (HR = 0.59; 95% CI: 0.19, 1.82). A substantial degree of correlation between relapse and death was observed, when both models were used.

In a previous analysis where the association between relapse and death has not been taken into consideration and disease-free survival (DFS) was the outcome of interest, the HR comparing patients on CRT and RT was 0.57 (95% CI: 0.38, 0.87).[4] A re-analysis of the data showed that when recurrence-free survival was of interest, the HR was 0.51 (95% CI: 0.32, 0.82). When overall survival was the outcome of interest, the HR was 0.51 (95% CI: 0.31, 0.81).[4] While the magnitudes of the HR for death were similar using the restrictive compartment model or the Cox proportional hazards assuming non-informative censoring, a slightly larger protective treatment effect for relapse was conferred by the restrictive compartment model. However, whereas statistical significance was achieved in the analyses by Wee *et al*[4], significance was not reached using either of the current parametric models.

Table 16: Parameter estimates based on the proposed Restrictive Compartment model (data from NPC trial by Wee *et al*.[4])

Parameters	Estimate	95% CI	exp(Estimate) (95% CI)
θ'	2.19	(1.84, 2.54)	8.96 (6.31, 12.72)
β_1	-0.87	(-1.98, 0.24)	0.42 (0.14, 1.27)†
β_2	-0.53	(-1.65, 0.60)	0.59 (0.19, 1.82)†
λ_1'	-0.05	(-0.39, 0.30)	0.95 (0.67, 1.34)
λ_2'	-0.70	(-1.01, -0.38)	0.50 (0.36, 0.68)
γ_1'	0.93	(0.72, 1.13)	2.52 (2.06, 3.09)
γ_2'	0.99	(0.79, 1.20)	2.70 (2.20, 3.32)

†: Corresponds to hazards ratio (HR)

Chapter 6: Discussion and Concluding remarks

In biomedical studies, it is often of interest to evaluate the efficacy of treatment in a clinical trial or the effect of covariates such as stage of cancer. Although death is an important endpoint, investigation of intermediate events, such as relapse, are also essential as they provide additional information pertaining to the disease progression process. In the ATAC trial data example, while 60% of the patients died after recurrence, the remaining 40% of the patients died without recurrence and from other causes. Although it is anticipated that recurrence is a relatively strong indicator for death, some of the death causes may not be disease-related, and therefore not strongly predicted by recurrence. Therefore, it will also be useful to know whether reducing morbidity will reduce mortality to the same extent. And if the effects of treatment are different for the two different types of outcomes (morbidity and mortality), it will be of interest to quantify the relative efficacy of treatment on both mortality and morbidity.

In addition, in cancer trials such as ATAC, radiotherapy is one of the usual treatment options for cancer patients. Although radiotherapy may be able to improve patient survival, its effect on normal tissue is not known. It will then be relevant to quantify the effect of the intermediate event (toxicity) by radiation, while accounting for the effect of radiotherapy on overall survival.[25] Therefore, this further corroborates the importance of looking at intermediate events in a disease progression process.

The type of survival data as mentioned above, where both morbidity (non-terminal event) and mortality (terminal event) are of analytical importance, has been defined earlier in this thesis as semi-competing risks data. Due to the lack of an appropriate methodology, semi-competing risks data are sometimes analyzed based on a competing risks framework where treatment efficacy is evaluated using only first-event information from each individual, ignoring all subsequent events that follow. In this instance, apart from describing the events using cumulative incidence functions[15,43], Cox proportional hazards model is also frequently fitted to obtain the cause-specific hazard ratio estimate of the exposure for each event conditional on surviving all other failure types. While this first-event only approach eliminates the need to address the association between multiple event times for the same subject, it is inefficient because it does not utilize all the available information[44]. This postulate is supported in a study by Tai *et al*[45], which showed discrepancies in hazard ratio estimates between methods which consider only the first event that occurs, and those that utilize information on all subsequent events. The discrepancies were magnified in instances when event times are highly correlated, or when the relative mean lifetime of the events are about equal. Besides, based on the competing risks paradigm, the dependence structure and the marginal distributions are not identifiable.[46] Although much effort has been devoted to bounding the marginals[47-49], these methods are complex and have assumptions that are not testable.

In view of the association between relapse and death, appropriate methodologies will be needed to profile the risk of morbidity and mortality over time more realistically, with emphasis on the non-terminal event. This need to map morbidity on the disease progression was corroborated by Fine *et al.*[7]. In comparison to their method which considers the association between the non-terminal and terminal events, it was observed that the Kaplan-Meier method consistently overestimated the survival curve for relapse. As a consequence, appreciable differences in the estimates for covariates can occur depending on whether dependent censoring has been accounted for[18,26,31]. This is illustrated by a difference in treatment effect for relapse in the NPC data as presented in Chapter 5 of this thesis, which was observed to be intensified as compared to the effects obtained by the naive Cox proportional hazards model assuming non-informative censoring in Wee *et al*[4]. In a similar study on nasopharyngeal cancer by Xu *et al*[31], which accounts for possible dependence between relapse and death via a non-parametric approach, a reduced risk of relapse was also observed in patients on CRT as compared with RT. In the latter study, the log-hazards of relapse among patients on CRT was -0.82 (SE: 0.34) times as much as those on RT. The log-hazards of death and relapse-to-death among patients on CRT were 0.14 (SE: 0.53) and -0.74 (SE: 0.35) times as much as patients on RT respectively. Their estimates were similar to those obtained in this thesis (Table 13), which suggested robustness of the parameter estimates against misspecification in the baseline hazard form. In another study by Peng[18], it was noted that the risk of first virologic failure amongst patients on Efavirenz (EFV) was 0.66 (Estimate (SE): -

0.416 (0.222)) times that of those on Nelfinavir (NFV) when Cox proportional hazards model was used without taking potentially dependent censoring of first virologic failure by death into account. When dependent censoring was considered, the estimate (SE) of the treatment effect became -0.487 (0.226), indicating that EFV put patients at a much lower risk of first virologic failure as compared to NFV (39% as compared to the previous 34%). Similarly, in the National Surgical Adjuvant Breast and Bowel Project (NSABP)[26], a difference in the effect of Tamoxifen on local-regional failure was observed, depending on whether possible dependent censoring of local-regional failure by distant failure, second primary cancers and non-cancer deaths was considered. When possible dependence was ignored, a HR of 0.411 (95% CI: 0.312, 0.541) was achieved. Accounting for possible dependence resulted in a HR of 0.528 (95% CI: 0.444, 0.627).

Methods for analyzing semi-competing risks data were proposed following Fine *et al*[7]. Assuming that the form of the marginal distribution for the time to the non-terminal event is known, approaches involving copula models and marginal distributions for the non-terminal event under weak assumptions have been put forth. However, in contrast to previous studies which have made assumptions about the marginal distribution for the time to the non-terminal outcome, no such assumption is made in this study and we limit our analysis to the observable region of the data. With observed pairs of morbidity and mortality data, we introduced a new method for semi-competing risks data to account for

the dependence structure between morbidity and mortality, while estimating their respective hazard functions using a frailty approach. We used the Clayton (gamma frailty) copula model in the joint modeling of morbidity and mortality because of its mathematical convenience, although more flexible models such as the Archimedean[21] and time-dependent[18] copulas may be adopted. We have not checked for the appropriateness in the usage of the Clayton copula model[26], but it has been suggested that the estimates remain fairly robust even when copulas are mis-specified.[25]

With the frailty model, covariate effects can be directly interpreted with explicit modeling of the baseline hazards via Cox proportional hazards model together with the association parameter between morbidity and mortality. This approach is similar to Xu *et al*[31], Peng and Fine[18] as well as Hsieh and Wang[30]. However, differences in the formulation of the regression models exist. While baseline hazards were assumed to be governed by a parametric form (Weibull distribution) in this thesis, a non-parametric method was used to describe the baseline hazards in Xu *et al*.[31] Although non-parametric hazards may offer more robust covariate estimates, parametric distributions offer a direct description of baseline hazards. Moreover, model fit could be easily checked using graphical techniques as suggested in Section 3. Furthermore, while Cox proportional hazards model was adopted for regression purposes in this thesis, Peng and Fine[18] as well as Hsieh and Wang[30], used a flexible monotone function, which

incorporates proportional hazards model as a special case, to describe the functional form for morbidity.

Among other differences in the model formulation as compared to previous methods, we have also allowed for model parameters to vary depending on the state of disease progression. This is illustrated by the construction of the compartment model in Section 3.1. Apart from varying effects of covariates on outcomes based on whether the patient has a previous occurrence of morbidity (e.g. relapse), baseline hazards also varied according to the progression of disease. This approach is generally more flexible than other methods proposed previously. This is because we think that the risk of death are likely to be different among patients who have experienced a relapse than those who have not, and this correlation between relapse and death may not have been fully accounted for by frailty. Therefore, the unaccounted "excess" correlation will be manifested as a difference in model parameterizations in the compartment model as shown in Section 3.1. Previous methods have assumed that any dependency between the non-terminal and terminal events has been fully captured by frailty. Hence, the strength of our method lies in the adoption of a more general model formulation according to the state of disease. A test of model parameters can also be performed, in order to determine if a less complex model results.

Computation of the model parameter estimates can be easily achieved using the NR algorithm. Simulation studies attested to the performance of the

proposed method, with small MSEs and CPs close to the nominal level. Checks of overall model adequacy are available with the implementation of the proposed method. One technique, such as that involving graphical assessment of the Cox-Snell residuals, has been suggested to establish model fit here. Through the Cox-Snell residuals, it was shown that a lack of fit was observed in the relapse-to-death path of the compartment model for NPC data. This was possibly due to the difference in the shape parameters governing the baseline hazards for the relapse-to-death arm in both RT and CRT, as shown by the subgroup analyses in Chapters 5. However, for the proposed model in this thesis, we have imposed the constraint that the shape and scale parameters determining the baseline hazards only depend on the pathway of the compartment model and not on the covariate (treatment). Nevertheless, we believe that if the baseline hazards were correctly specified, the proposed model would work well in practical settings, as attested by the simulation results. Hence, other models with more suitable parametric baseline hazards could be considered when a lack of fit in the data was observed.

The importance of accounting for the dependency between relapse and death was shown in both the simulated and NPC datasets. The magnitude of the dependency serves as an indication of the predictive value that an occurrence of relapse will have on death. If the dependency is strong, it implies that an occurrence of relapse will increase the risk of mortality substantially. Conversely, if the dependency is almost negligible, then it suggests that the prognostic outlook will probably not change even if a relapse were to occur. Referring to the scenario

relating to relapse and death at the beginning of this chapter, if there was indeed an association of substantial magnitude between these two events, it would then be necessary to develop or adopt appropriate treatment strategies which could lower the chances of relapse, since it would influence the progression to death.

The proposed compartment model fits the structure of semi-competing risks data nicely, and provides an interpretable estimation of the covariate effects on morbidity. However, one limitation of the compartment model is that while the overall survival probability for the terminal event can be estimated using conventional methods, the survival probability for the non-terminal outcomes is not estimable as we do not assume that the form of the distribution on the lower wedge (where the non-terminal is censored by the terminal event) to be known.

The current compartment model may be generalized to accommodate other forms of settings. In the proposed compartment model approach, we have assumed only one non-terminal event occurring before the terminal event. However, scenarios may arise which warrant investigation of the inter-relationships between more than one non-terminal event, in addition to the possible occurrence of the terminal event. Local recurrence has been demonstrated to be an important indicator for metastasis; and survival patterns for metastatic breast cancer patients depend on whether local recurrence has occurred previously. However, prognostic outlooks may be different for women who have metastases at different anatomical locations[50]. Hence, it will be useful to explore

how the current proposed model can be further generalized to take into account all possible types of clinically important intermediate events which can occur before the occurrence of the terminal event.

The current model also assumes that the covariate effects and the parameter estimates are time-invariant. However, the dependence between event times, as well as the covariate effects, may vary over time. Therefore, studies on how to employ techniques involving time-dependent copulas, such as that proposed in Peng and Fine[18], for modeling the dependence between non-terminal and terminal event times will be required. Furthermore, the current compartment model was proposed for right-censored data, such as that observed in a usual clinical trials setting. However, data subjected to left truncation and right censoring, such as those involving registries, may arise[27]. Hence, it will be useful to investigate how the current proposed model can be extended to accommodate data of this structure.

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Appendix:

The score equations and elements of the information matrix are written explicitly below.

First, define:

$m_1 = (\lambda_1 t_1)^{\gamma_1} \exp(\beta_1 X)$; $m_2 = (\lambda_2 t_1)^{\gamma_2} \exp(\beta_2 X)$; $m_3 = (\lambda_3 t_2)^{\gamma_3} \exp(\beta_3 X)$;
$m_4 = (\lambda_3 t_1)^{\gamma_3} \exp(\beta_3 X)$.
$m = m_1 + m_2 + m_3 - m_4$
$k = 1 + m\theta$
$e = \frac{1}{\theta} + \delta_1 + \delta_2$

Score Equations:

$$\frac{\partial \ell}{\partial \theta} = \frac{\delta_1 \delta_2}{1+\theta} - \frac{em}{k} + \frac{1}{\theta^2}\log(k)$$
$$\frac{\partial \ell}{\partial \beta_1} = \delta_1 X - \frac{e\theta X m_1}{k}$$
$$\frac{\partial \ell}{\partial \beta_2} = (1-\delta_1)\delta_2 X - \frac{e\theta X m_2}{k}$$
$$\frac{\partial \ell}{\partial \beta_3} = \delta_1 \delta_2 X - \frac{e\theta X (m_3 - m_4)}{k}$$
$$\frac{\partial \ell}{\partial \lambda_1} = \frac{\delta_1 \gamma_1}{\lambda_1} - \frac{e\gamma_1 m_1}{\lambda_1 k}$$
$$\frac{\partial \ell}{\partial \lambda_2} = \frac{(1-\delta_1)\delta_2 \gamma_2}{\lambda_2} - \frac{e\gamma_2 m_2}{\lambda_2 k}$$
$$\frac{\partial \ell}{\partial \lambda_3} = \frac{\delta_1 \delta_2 \gamma_3}{\lambda_3} - \frac{e\gamma_3 (m_3 - m_4)}{\lambda_3 k}$$
$$\frac{\partial \ell}{\partial \gamma_1} = \frac{\delta_1}{\gamma_1} + \delta_1 \log(\lambda_1 t_1) - \frac{e\theta m_1 \log(\lambda_1 t_1)}{k}$$

$$\frac{\partial \ell}{\partial \gamma_2} = \frac{(1-\delta_1)\delta_2}{\gamma_2} + (1-\delta_1)\delta_2 \log(\lambda_2 t_2) - \frac{e\theta m_2 \log(\lambda_2 t_1)}{k}$$
$$\frac{\partial \ell}{\partial \gamma_3} = \frac{\delta_1\delta_2}{\gamma_3} + \delta_1\delta_2 \log(\lambda_3 t_2) - \frac{e\theta(m_3 \log(\lambda_3 t_2) - m_4 \log(\lambda_3 t_1))}{k}$$

Information Matrix:

$$\frac{\partial^2 \ell}{\partial \theta^2} = -\frac{\delta_1\delta_2}{(1+\theta)^2} + \frac{em^2}{k^2} + \frac{2m}{\theta^2 k} - \frac{2}{\theta^3}\log(k)$$
$$\frac{\partial^2 \ell}{\partial \theta \partial \beta_1} = -\frac{eXm_1}{k^2} + \frac{Xm_1}{\theta k}$$
$$\frac{\partial^2 \ell}{\partial \theta \partial \beta_2} = -\frac{eXm_2}{k^2} + \frac{Xm_2}{\theta k}$$
$$\frac{\partial^2 \ell}{\partial \theta \partial \beta_3} = -\frac{eX(m_3-m_4)}{k^2} + \frac{X(m_3-m_4)}{\theta k}$$
$$\frac{\partial^2 \ell}{\partial \theta \partial \lambda_1} = -\frac{e\gamma_1 m_1}{\lambda_1 k^2} + \frac{\gamma_1 m_1}{\lambda_1 \theta k}$$
$$\frac{\partial^2 \ell}{\partial \theta \partial \lambda_2} = -\frac{e\gamma_2 m_2}{\lambda_2 k^2} + \frac{\gamma_2 m_2}{\lambda_2 \theta k}$$
$$\frac{\partial^2 \ell}{\partial \theta \partial \lambda_3} = -\frac{e\gamma_3(m_3-m_4)}{\lambda_3 k^2} + \frac{\gamma_3(m_3-m_4)}{\lambda_3 \theta k}$$
$$\frac{\partial^2 \ell}{\partial \theta \partial \gamma_1} = -\frac{em_1 \log(\lambda_1 t_1)}{k^2} + \frac{m_1 \log(\lambda_1 t_1)}{\theta k}$$
$$\frac{\partial^2 \ell}{\partial \theta \partial \gamma_2} = -\frac{em_2 \log(\lambda_2 t_1)}{k^2} + \frac{m_2 \log(\lambda_2 t_1)}{\theta k}$$
$$\frac{\partial^2 \ell}{\partial \theta \partial \gamma_3} = -\frac{e(m_3 \log(\lambda_3 t_2) - m_4 \log(\lambda_3 t_1))}{k^2} + \frac{m_3 \log(\lambda_3 t_2) - m_4 \log(\lambda_3 t_1)}{\theta k}$$

$$\frac{\partial^2 \ell}{\partial \beta_1^2} = -\frac{e\theta X^2 m_1(k - m_1\theta)}{k^2}$$
$$\frac{\partial^2 \ell}{\partial \beta_1 \partial \beta_2} = \frac{e\theta^2 X^2 m_1 m_2}{k^2}$$
$$\frac{\partial^2 \ell}{\partial \beta_1 \partial \beta_3} = \frac{e\theta^2 X^2 m_1(m_3-m_4)}{k^2}$$

$$\frac{\partial^2 \ell}{\partial \beta_1 \partial \lambda_1} = -\frac{e\theta X \gamma_1 m_1 (k - m_1 \theta)}{\lambda_1 k^2}$$
$$\frac{\partial^2 \ell}{\partial \beta_1 \partial \lambda_2} = \frac{e\theta^2 X \gamma_2 m_1 m_2}{\lambda_2 k^2}$$
$$\frac{\partial^2 \ell}{\partial \beta_1 \partial \lambda_3} = \frac{e\theta^2 X \gamma_3 m_1 (m_3 - m_4)}{\lambda_3 k^2}$$
$$\frac{\partial^2 \ell}{\partial \beta_1 \partial \gamma_1} = -\frac{e\theta X m_1 (k - m_1 \theta) \log(\lambda_1 t_1)}{k^2}$$
$$\frac{\partial^2 \ell}{\partial \beta_1 \partial \gamma_2} = \frac{e\theta^2 X m_1 m_2 \log(\lambda_2 t_1)}{k^2}$$
$$\frac{\partial^2 \ell}{\partial \beta_1 \partial \gamma_3} = \frac{e\theta^2 X m_1 (m_3 \log(\lambda_3 t_2) - m_4 \log(\lambda_3 t_1))}{k^2}$$

$$\frac{\partial^2 \ell}{\partial \beta_2^{\,2}} = -\frac{e\theta X^2 m_2 (k - m_2 \theta)}{k^2}$$
$$\frac{\partial^2 \ell}{\partial \beta_2 \partial \beta_3} = \frac{e\theta^2 X^2 m_2 (m_3 - m_4)}{k^2}$$
$$\frac{\partial^2 \ell}{\partial \beta_2 \partial \lambda_1} = \frac{e\theta^2 X \gamma_1 m_1 m_2}{\lambda_1 k^2}$$
$$\frac{\partial^2 \ell}{\partial \beta_2 \partial \lambda_2} = -\frac{e\theta X \gamma_2 m_2 (k - m_2 \theta)}{\lambda_2 k^2}$$
$$\frac{\partial^2 \ell}{\partial \beta_2 \partial \lambda_3} = \frac{e\theta^2 X \gamma_3 m_2 (m_3 - m_4)}{\lambda_3 k^2}$$
$$\frac{\partial^2 \ell}{\partial \beta_2 \partial \gamma_1} = \frac{e\theta^2 X m_1 m_2 \log(\lambda_1 t_1)}{k^2}$$
$$\frac{\partial^2 \ell}{\partial \beta_2 \partial \gamma_2} = -\frac{e\theta X m_2 (k - m_2 \theta) \log(\lambda_2 t_1)}{k^2}$$
$$\frac{\partial^2 \ell}{\partial \beta_2 \partial \gamma_3} = \frac{e\theta^2 X m_2 (m_3 \log(\lambda_3 t_2) - m_4 \log(\lambda_3 t_1))}{k^2}$$

$$\frac{\partial^2 \ell}{\partial \beta_3^{\,2}} = -\frac{e\theta X^2 (m_3 - m_4)(k - (m_3 - m_4)\theta)}{k^2}$$
$$\frac{\partial^2 \ell}{\partial \beta_3 \partial \lambda_1} = \frac{e\theta^2 X \gamma_1 m_1 (m_3 - m_4)}{\lambda_1 k^2}$$
$$\frac{\partial^2 \ell}{\partial \beta_3 \partial \lambda_2} = \frac{e\theta^2 X \gamma_2 m_2 (m_3 - m_4)}{\lambda_2 k^2}$$

$$\frac{\partial^2 \ell}{\partial \beta_3 \partial \lambda_3} = -\frac{e\theta X \gamma_3 (m_3 - m_4)(k - (m_3 - m_4)\theta)}{\lambda_3 k^2}$$
$$\frac{\partial^2 \ell}{\partial \beta_3 \partial \gamma_1} = \frac{e\theta^2 X (m_3 - m_4) m_1 \log(\lambda_1 t_1)}{k^2}$$
$$\frac{\partial^2 \ell}{\partial \beta_3 \partial \gamma_2} = \frac{e\theta^2 X (m_3 - m_4) m_2 \log(\lambda_2 t_1)}{k^2}$$
$$\frac{\partial^2 \ell}{\partial \beta_3 \partial \gamma_3} = -\frac{e\theta X (m_3 \log(\lambda_3 t_2) - m_4 \log(\lambda_3 t_1))(k - (m_3 - m_4)\theta)}{k^2}$$

$$\frac{\partial^2 \ell}{\partial \lambda_1^2} = -\frac{\delta_1 \gamma_1}{\lambda_1^2} - \frac{e\theta\gamma_1(((\gamma_1 - 1)km_1) - (\theta\gamma_1 m_1^2))}{\lambda_1^2 k^2}$$
$$\frac{\partial^2 \ell}{\partial \lambda_1 \partial \lambda_2} = \frac{e\theta^2 \gamma_1 \gamma_2 m_1 m_2}{\lambda_1 \lambda_2 k^2}$$
$$\frac{\partial^2 \ell}{\partial \lambda_1 \partial \lambda_3} = \frac{e\theta^2 \gamma_1 \gamma_3 m_1 (m_3 - m_4)}{\lambda_1 \lambda_3 k^2}$$
$$\frac{\partial^2 \ell}{\partial \lambda_1 \partial \gamma_1} = \frac{\delta_1}{\lambda_1} - e\theta m_1 \frac{(k(1 + \gamma_1 \log(\lambda_1 t_1)) - (\gamma_1 \theta m_1 \log(\lambda_1 t_1)))}{\lambda_1 k^2}$$
$$\frac{\partial^2 \ell}{\partial \lambda_1 \partial \gamma_2} = \frac{e\theta^2 \gamma_1 m_1 m_2 \log(\lambda_2 t_1)}{\lambda_1 k^2}$$
$$\frac{\partial^2 \ell}{\partial \lambda_1 \partial \gamma_3} = \frac{e\theta^2 \gamma_1 m_1 (m_3 \log(\lambda_3 t_2) - m_4 \log(\lambda_3 t_2))}{\lambda_1 k^2}$$

$$\frac{\partial^2 \ell}{\partial \lambda_2^2} = -\frac{(1 - \delta_1)\delta_2 \gamma_2}{\lambda_2^2} - \frac{e\theta\gamma_2(((\gamma_2 - 1)km_2) - (\theta\gamma_2 m_2^2))}{\lambda_2^2 k^2}$$
$$\frac{\partial^2 \ell}{\partial \lambda_2 \partial \lambda_3} = \frac{e\theta^2 \gamma_2 \gamma_3 m_2 (m_3 - m_4)}{\lambda_2 \lambda_3 k^2}$$
$$\frac{\partial^2 \ell}{\partial \lambda_2 \partial \gamma_1} = \frac{e\theta^2 \gamma_2 m_1 m_2 \log(\lambda_1 t_1)}{\lambda_2 k^2}$$
$$\frac{\partial^2 \ell}{\partial \lambda_2 \partial \gamma_2} = \frac{(1 - \delta_1)\delta_2}{\lambda_2} - e\theta m_2 \frac{(k(1 + \gamma_2 \log(\lambda_2 t_1)) - (\gamma_2 \theta m_2 \log(\lambda_2 t_1)))}{\lambda_2 k^2}$$
$$\frac{\partial^2 \ell}{\partial \lambda_2 \partial \gamma_3} = \frac{e\theta^2 \gamma_2 m_2 (m_3 \log(\lambda_3 t_2) - m_4 \log(\lambda_3 t_1))}{\lambda_2 k^2}$$

$$\frac{\partial^2 \ell}{\partial \lambda_3^2} = -\frac{\delta_1 \delta_2 \gamma_3}{\lambda_3^2} - \frac{e\theta\gamma_3(((\gamma_3 - 1)k(m_3 - m_4)) - (\theta\gamma_3(m_3 - m_4)^2))}{\lambda_3^2 k^2}$$

$$\frac{\partial^2 \ell}{\partial \lambda_3 \partial \gamma_1} = \frac{e\theta^2 \gamma_3 m_1 (m_3 - m_4) \log(\lambda_1 t_1)}{\lambda_3 k^2}$$

$$\frac{\partial^2 \ell}{\partial \lambda_3 \partial \gamma_2} = \frac{e\theta^2 \gamma_3 m_2 (m_3 - m_4) \log(\lambda_2 t_1)}{\lambda_3 k^2}$$

$$\frac{\partial^2 \ell}{\partial \lambda_3 \partial \gamma_3} = \frac{\delta_1 \delta_2}{\lambda_3} - e\theta \frac{k(m_3 - m_4) + \gamma_3 (m_3 \log(\lambda_3 t_2) - m_4 \log(\lambda_3 t_1))(k - (m_3 - m_4)\theta)}{\lambda_3 k^2}$$

$$\frac{\partial^2 \ell}{\partial \gamma_1^2} = -\frac{\delta_1}{\gamma_1^2} - e\theta m_1 (\log(\lambda_1 t_1))^2 \frac{k - m_1 \theta}{k^2}$$

$$\frac{\partial^2 \ell}{\partial \gamma_1 \partial \gamma_2} = \frac{e\theta^2 m_1 m_2 \log(\lambda_1 t_1) \log(\lambda_2 t_1)}{k^2}$$

$$\frac{\partial^2 \ell}{\partial \gamma_1 \partial \gamma_3} = \frac{e\theta^2 m_1 \log(\lambda_1 t_1)(m_3 \log(\lambda_3 t_2) - m_4 \log(\lambda_3 t_1))}{k^2}$$

$$\frac{\partial^2 \ell}{\partial \gamma_2^2} = -\frac{(1 - \delta_1)\delta_2}{\gamma_2^2} - e\theta m_2 (\log(\lambda_2 t_1))^2 \frac{k - m_2 \theta}{k^2}$$

$$\frac{\partial^2 \ell}{\partial \gamma_2 \partial \gamma_3} = \frac{e\theta^2 m_2 \log(\lambda_2 t_1)(m_3 \log(\lambda_3 t_2) - m_4 \log(\lambda_3 t_1))}{k^2}$$

$$\frac{\partial^2 \ell}{\partial \gamma_3^2} = -\frac{\delta_1 \delta_2}{\gamma_3^2} - e\theta \frac{(k(m_3 \log(\lambda_3 t_2)^2 - m_4 \log(\lambda_3 t_1)^2)) - (\theta(m_3 \log(\lambda_3 t_2) - m_4 \log(\lambda_3 t_1)))^2}{k^2}$$