COMPETING RISKS REGRESSION UNDER RANDOM SIGNS CENSORING USING PSEUDO-VALUES

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ABSTRACT

In medical research, investigators are often interested in estimating marginal survival distributions of latent failure times in the presence of competing risks. However, marginal survival functions are not identifiable without further assumption. Previous studies have shown that by incorporating the random signs censoring (RSC) principle, we can estimate marginal survival functions and that the RSC principle is verifiable from the observed data.

In this study, we proposed under the RSC principle an estimator of covariate effect on marginal survival function using time-dependent pseudo-values created from inverse-probability-censoring-weighted (IPCW) Kaplan-Meier estimates. A generalized linear regression model of pseudo-values can then be built, from which the covariate effects and marginal survival at any given time can be estimated by solving the corresponding generalized estimating equations. Time-dependent covariates are easy to incorporate in our method. We also derived robust standard errors of the estimators, examined the asymptotic properties, and developed a graphical representation for changes in covariate effects over time.

We evaluated the finite-sample performance of the estimator and the corresponding marginal survival estimators via simulation studies. In applications of the proposed method, we identified potential risk factors of pretransplantation survival for pediatric patients with end-stage liver diseases and estimated their 90-day pretransplantation survival graphically. Effects of time-varying covariates were estimated and the covariate effects against time were

also examined graphically. **Public Health Significance:** Our proposed method is easier for statisticians to implement and the analysis results are easier for medical professionals to interpret. The proposed method allows medical researchers to incorporate repeatedly measured covariates as well as constant covariates and evaluate time-varying covariate effects in the presence of competing risks, which eliminates certain biases in estimating marginal survival and in turn can contribute to better policy or regulatory decisions.

Keywords: Competing risks; inverse probability censoring weight; marginal survival function; pseudo-values; random signs censoring; risk prediction.

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1.0 INTRODUCTION

In medical and epidemiological studies, competing risks arise when subjects are at risk of failing from multiple causes and one cause precludes observing the others or alters the probabilities of occurrence of the others. For instance, individuals may dropout or die from causes other than the one of interest. Quantities used to describe such type of data include the cumulative incidence function (CIF), which is also known as subdistribution, cause-specific hazards (CSH), and marginal survival functions. The CIF represents the cumulative probability of failing from the event of interest by time t in the presence of other types of failure. The instantaneous failure rate of the cause of interest is characterized by the CSH, where the competing events are treated as non-informative censoring. Marginal survival function is defined as the probability of surviving from the cause of interest by time t in a world where all other risks are absent. This quantity is particularly appealing when the scientific problems involve finding the 'pure' or 'net' effect of some covariates on survival. For example, the transplantation community has always been interested in designing a prioritized organ allocation algorithm based on the risk factors associated with the underlying mortality process. However, patients may experience other events such as transplantation. Therefore, to identify the risk factors, analyses should focus on marginal distributions of the death time rather than crude distributions, i.e., CIF. A well-known issue is that the observed data provides insufficient information to characterize the joint distribution of the competing event times. Also, it is no longer reasonable to assume independence between death and transplantation since sicker patients have higher priority to receive transplant, indicating a positive relationship. Tsiatis (1975) pointed out that different sets of marginal distributions may lead to the same joint distribution and independent risk model is indistinguishable from dependent risk model, which is known as the non-identifiability problem. Therefore, having

the observed data alone is not sufficient to identify the marginal distributions of the latent variables if their dependence structure is unknown.

In practice, competing risks are often assumed to be independent events and considered as non-informative censoring, assuming that the distribution of the event times of interest provides no information about the distribution of the censoring times in analysis. Standard estimators such as Kaplan-Meier and Nelson-Aalen or Cox proportional hazards model under a regression setting can yield marginal distribution of the main event (Yabes, 2012). However, independence of the risks is not always true, especially lack of biological basis in medical field. Thus, assumptions on dependence structure of the competing risks are needed. If one is not willing to impose an assumption to identify the relationship between the main event and competing events, it is only possible to obtain bounds for the marginal distributions (Peterson, 1976). Moeschberger (1974) proposed a joint model of two lifetime distributions using a shared random effect, known as frailty, to capture the dependence structure of the failure times. Copula-based models that allow for different types of dependence structure of risks are widely used. Zheng and Klein (1995) derived nonparametric estimators of the marginal distribution and bounds of survival function can be obtained given a range of strengths of the association between competing risks using this approach, which is also robust to specification of the functional form. This work was later extended to deal with more than two competing events (Escarela and Carriere, 2003; Lo and Wilke, 2010). Yabes (2012) introduced random signs censoring (RSC) principle into the framework of semiparametric competing risks models. The RSC assumes that the main event will occur before the competing event is independent of the distribution of the main event time. Unlike the imposed assumptions in practice, RSC is verifiable from the observed data. Also, this new approach is easy to implement in the Cox proportional hazards model and accommodates noninformative censoring.

We propose a generalized regression model which can be used to analyze competing risks data under random signs censoring using pseudo-values. The pseudo-values method (*aka* pseudo-observation method) is adapted from the jackknife methods, developed by Quenouille as a nonparametric approach to estimate and reduce bias of the estimators (Quenouille, 1956). The basic idea is to calculate pseudo-values for nonparametric estimators,

such as the *Kaplan-Meier estimator*, using leave-one-out statistics. These pseudo-values calculated at a set of selected time points are used in a generalized linear model to regress marginal survival on the potential risk factors. We then solve the corresponding generalized estimating equation (GEE) to obtain the estimated covariate effects. Andersen et al. (2003) first suggested to adopt pseudo-values to model the state probabilities directly through Aalen-Johansen estimator. Unlike other multistate regression analysis in which models are frequently specified via transition intensities, pseudo-values approach allows for estimation of covariate effects on state probabilities or transition probabilities in generalized linear models. This technique was applied to the comparison of survival probabilities among several groups at a fixed point in time. In addition to the naive tests or the Mantel-Haenszel test, pseudo-values can accommodate the inclusion of explanatory variables in stratified analysis (Klein et al., 2007). It also provides an alternative approach to estimate covariate effects on the mean survival time and the restricted mean survival time (Andersen et al., 2004). Klein and Andersen (2005) proposed to perform regression analysis of competing risks data based on pseudo-values of the CIF. Their presented method is similar to that proposed by Fine (2001) but more flexible with choices on link functions, regression models, and working correlation matrices. Furthermore, pseudo-residuals based on pseudo-values were defined and are used to provide graphical evaluation of the fitted regression models including the linearity assumption and constant effect over time (Perme and Andersen, 2008).

Our goal is to estimate marginal failure function for the event of interest while accommodating positively associated competing risks and noninformative censoring. To achieve the goal, we first remove individuals who experienced competing events from the original dataset under the random signs censoring assumption. We then derive inverse probability of censoring weights (IPCW) from the data, and apply the pseudo-values approach to generate a weighted pseudo complete dataset based on the weighted Kaplan-Meier estimator; in the last step, individuals with noninformative censoring are "imputed." This weighted pseudo complete dataset may later be used to investigate potential risk factors and to estimate absolute risk by fitting a generalized linear regression model with GEE. In this type of analysis, pseudo-values can be calculated at all time points for all individuals.

The dissertation is organized as follows. In Section 2, we lay out the notation, describe our proposed estimator, and provide proof of its consistency and asymptotic normality. In Section 3, we investigate the finite sample properties of the proposed procedure in terms of bias, standard error, standard deviation, and empirical coverage probability through simulations. In Section 4 we illustrate the methods with the liver transplant data and some concluding remarks and further discussion are found in Section 5.

2.0 METHOD

2.1 NOTATION

Without loss of generality, we will consider two failure types. Let (T_1, T_2) and C be the failure and noninformative censoring times; where $\epsilon = I(T_1 \leq T_2)$ denotes the cause of failure; and where T_1 is the event time of interest ($\epsilon = 1$) and T_2 the event time of competing risk ($\epsilon = 0$). Let $\boldsymbol{Z}$ be p-dimensional covariates. Suppose we have $i \in \{1, \ldots, n\}$ independent subjects and let $T_i = T_{1i} \wedge T_{2i}$. Define the marginal distribution function and marginal survival function of the main event as $F_1(t) = Pr(T_1 \leq t)$ and $S_1(t) = Pr(T_1 > t) = 1 - F_1(t)$, respectively. The subdistribution function for T_1 is defined by $F_1(t) = Pr(T \leq t, \epsilon = 1)$. The conditional distribution functions (also referred to as normalized subdistribution functions) for T_1 and T_2 are $\tilde{F}_1(t) = Pr(T_1 \leq t | T_1 < T_2)$ and $\tilde{F}_2(t) = Pr(T_2 \leq t | T_2 < T_1)$, respectively.

For the usual right-censored data, we observe $(\tilde{X}_i, \delta_i, \epsilon_i, Z_i)$, where $\tilde{X}_i = T_i \wedge C_i,\ \delta_i = I(T_i \leq C_i)$ and $I(\cdot)$ is the indicator function. Define the counting process $\tilde{N}_{i1}(t) = I(\tilde{X}_i \leq t, \delta_i = 1, \epsilon_i = 1)$ and the at risk process $\tilde{Y}_{i1}(t) = I(\tilde{X}_i \geq t, \delta_i = 1, \epsilon_i = 1)$ based on the observed data.

2.2 COMPETING RISKS AND RANDOM SIGNS CENSORING

Yabes (2012) applied the notion of random signs censoring (RSC) to accommodate positively dependent competing risks in semiparametric survival analysis. Event time T_2 is called a random signs censoring of T_1 if $I(T_1 < T_2)$ is stochastically independent of T_1. Under this assumption, the marginal distribution of main event time is identifiable, even though that

of the competing event time is not (Yabes, 2012). It follows that

$$\tilde{F}_1(t) = Pr(T_1 \leq t | T_1 < T_2) = F_1(t).$$

Therefore, the marginal distribution of T_1 is the same as its normalized subdistribution.

It was shown by Cooke (1993) that T_2 is RSC of T_1 if and only if $\tilde{S}_1(t) = 1 - \tilde{F}_1(t) > \tilde{S}_2(t) = 1 - \tilde{F}_2(t)$. A graphical approach can be applied to look for stochastic ordering in a plot of the estimated normalized subsurvival functions. If the estimated normalized subsurvival function of the main event dominates that of the competing event, then RSC is a reasonable assumption.

To estimate the marginal survival in the presence of independent censoring, the principles of inverse probability censoring weight (IPCW) can be adopted. We note that

$$E\Big\{\frac{1}{n}\sum_{i=1}^{n}\frac{\delta_i}{G(\tilde{X}_i)}I(\tilde{X}_i \in [t, t+dt), \epsilon_i = 1)\Big\} = Pr\{T \in [t, t+dt), \epsilon = 1\}$$

and

$$E\Big\{\frac{1}{n}\sum_{i=1}^{n}\frac{\delta_i}{G(\tilde{X}_i)}I(\tilde{X}_i \geq t, \epsilon_i = 1)\Big\} = Pr\{T \geq t, \epsilon = 1\}.$$

where $G(\cdot)$ is the survival function of censoring time.
This implies that

$$\frac{\frac{1}{n}\sum_{i=1}^{n}\frac{\delta_i}{G(\tilde{X}_i)}I(\tilde{X}_i \geq t, \epsilon_i = 1)}{\frac{1}{n}\sum_{i=1}^{n}\frac{\delta_i}{G(\tilde{X}_i)}I(\tilde{X}_i \geq t, \epsilon_i = 1)} \xrightarrow{a.s.} \frac{Pr\{T \in [t, t+dt), \epsilon = 1\}}{Pr\{T \geq t, \epsilon = 1\}} \tag{2.1}$$

$$= \frac{Pr\{T \in [t, t+dt), \epsilon = 1\}/Pr(\epsilon = 1)}{Pr\{T \geq t, \epsilon = 1\}/Pr(\epsilon = 1)}, \tag{2.2}$$

The right-hand quantity specified above is the hazard function of the normalized subsurvival distribution as $dt \to 0$. Under RSC, given that $T_1 \perp \epsilon = I(T_1 \leq T_2)$, we can show that

$$\frac{Pr\{T \in [t, t+dt), \epsilon = 1\}/Pr(\epsilon = 1)}{Pr\{T \geq t, \epsilon = 1\}/Pr(\epsilon = 1)} = \frac{Pr\{T_1 \in [t, t+dt)\}/Pr(\epsilon = 1)}{Pr\{T_1 \geq t\}/Pr(\epsilon = 1)},$$

which is the marginal hazard function $\lambda_1(t)$ that can be formulated as follows:

$$\begin{aligned}\lambda_1(t;\boldsymbol{Z}) &= \lim_{dt\to 0}\frac{1}{dt}Pr\{T_1\in[t,t+dt)|T_1\geq t,\boldsymbol{Z}\}\\ &= \lim_{dt\to 0}\frac{1}{dt}\frac{Pr\{T_1\in[t,t+dt),\boldsymbol{Z}\}}{Pr\{T_1\geq t,\boldsymbol{Z}\}}\\ &= -\frac{dS_1(t;\boldsymbol{Z})/dt}{S_1(t;\boldsymbol{Z})}\\ &= -\frac{d}{dt}\log\{S_1(t;\boldsymbol{Z})\}\end{aligned}$$

This implies that left-hand quantity in (2.1) can be validly applied to calculate marginal survival function.

Given that the Kaplan-Meier estimator is a consistent estimator for survival function (Andersen et al., 1995), the marginal survival function $S_1(t)$ can be estimated by

$$\hat{\tilde{S}}_1(t)=\prod_{s\leq t}\Big[1-\frac{\sum_{i=1}^n w_i(\tilde{X}_i)\,d\{I(\tilde{X}_i\leq s,\epsilon_i=1)\}}{\sum_{i=1}^n w_i(\tilde{X}_i)\,I(\tilde{X}_i\geq s,\epsilon_i=1)}\Big],$$

where $w_i(\tilde{X}_i)=\delta_i/\hat{G}(\tilde{X}_i)$ and $\hat{G}(\cdot)$ is the Kaplan-Meier estimate of the censoring time. We call this estimator IPCW Kaplan-Meier estimator for the main event under RSC.

2.3 CENSORING AND PSEUDO-VALUES METHOD

Noninformative right censoring is often encountered in survival data. Under this setting, only partial information is known for subjects with censoring, that the event will occur after the observed censoring times. In the following, we will define pseudo-values for each individual in order to create a pseudo complete dataset.

Let T be a random variable and $\theta=E\{f(T)\}$ be a quantity of interest, which is the expected value of some functions $f(\cdot)$; and $\hat{\theta}$ is an unbiased estimator of θ. For complete data, $\hat{\theta}_i=n^{-1}\cdot\sum_i f(T_i)$. For data with censoring, if the unbiased estimator $\hat{\theta}$ is available, the pseudo-values for $f(T)$ for individual i, $i=1,\ldots,n$, is then defined as

$$\hat{\theta}_i=n\cdot\hat{\theta}-(n-1)\cdot\hat{\theta}^{-i},$$

where $\hat{\theta}^{-i}$ is computed based on the reduced sample $T_1, \ldots, T_{i-1}, T_{i+1}, \ldots, T_n$. Pseudo-values are defined at all times for all individuals, thus being two-dimensional estimators $\hat{\theta}_i(t)$. To estimate covariate effect on marginal survival, pseudo-values $\hat{\theta}_i(t)$ can be calculated and then used as an outcome variable in a generalized linear regression model with some link function $g(\cdot)$:

$$g\{E(f(X)|\boldsymbol{Z})\} = \beta_0 + \sum \beta_p Z_p,$$

where β_0 and β_p are the unknown regression parameters need to be estimated.

In this study, the quantity of interest is the estimated marginal survival function with the form

$$\hat{\tilde{S}}_1(t) = \prod_{s \le t} \Big[1 - \frac{\sum_{i=1}^n w_i(\tilde{X}_i)\, d\{I(\tilde{X}_i \le s, \epsilon_i = 1)\}}{\sum_{i=1}^n w_i(\tilde{X}_i)\, I(\tilde{X}_i \ge s, \epsilon_i = 1)}\Big]. \tag{2.3}$$

To obtain pseudo-values from the data, we first denote $\hat{G}^{-i}$ the Kaplan-Meier estimator of the censoring time with the ith weight set to be 0. Therefore, the corresponding IPCW Kaplan-Meier estimator without the ith observation can be defined as:

$$\hat{\tilde{S}}_1^{-i}(t) = \prod_{s \le t} \Big[1 - \frac{\sum_{j \ne i} w_j^{-i}(\tilde{X}_j)\, d\{I(\tilde{X}_j \le s, \epsilon_j = 1)\}}{\sum_{j \ne i} w_j^{-i}(\tilde{X}_j)\, I(\tilde{X}_j \ge s, \epsilon_j = 1)}\Big], \tag{2.4}$$

where $w_j^{-i}(\tilde{X}_j) = \delta_j / \hat{G}^{(-i)}(\tilde{X}_j)$ is the weight function. For subject i, we define the jackknife pseudo-value at time t as follows:

$$J_{i,1}(t) = n\hat{\tilde{S}}_1(t) - (n-1)\hat{\tilde{S}}_1^{-i}(t). \tag{2.5}$$

The pseudo-value is constructed under two assumptions: First, the censoring time C_i is stochastically independent of (T_i, ϵ_i, Z_i). Second, the pseudo-values are defined only for time points $t < \tau$ such that $G(\tau) > \nu > 0$.

2.4 MODEL AND ESTIMATION

To analyze the effects of factors such as treatment types, age, or gender on marginal survival, the pseudo-values can be served as outcome variables in a generalized linear model with the form

$$S_1(t|\boldsymbol{Z}) = g^{-1}\{\beta_{0,1}(t) + \sum_{l=1}^{p} \beta_{l,1} Z_{li}\} = g^{-1}(\boldsymbol{\beta_{t,1}^T Z}),$$

where $\beta_{0,1}(t)$ is the log baseline hazard function at time t; $\boldsymbol{\beta_{l,1}}$ are the unknown regression coefficients; and $g(\cdot)$ is a specified link function. When c-log-log link function $g(y) = \log\{-\log(1-y)\}$ is used, the model is equivalent to a Cox proportional hazards model. The unknown regression coefficients can be solved from the following generalized estimating equation (GEE):

$$U_{(n)}(\boldsymbol{\beta_{t,1}}) = \sum_{i=1}^{n} [\frac{\partial}{\partial \boldsymbol{\beta_{t,1}}} g^{-1}(\boldsymbol{\beta_{t,1}}^T \boldsymbol{Z_i})]^T V_{it,1}^{-1} [J_{i,1}(t) - g^{-1}(\boldsymbol{\beta_{t,1}}^T \boldsymbol{Z_i})] = 0, \tag{2.6}$$

where $V_{it,1}$ is the usual "working covariance" matrix.

In addition to the usual regularity conditions, the following *asymptotic unbiasedness* of the pseudo-values is also required to solve equation (2.5):

$$E\{J_{i,1}(t)|Z_i\} = g^{-1}(\boldsymbol{\beta_{t,1}}^T \boldsymbol{Z}) + o_P(1). \tag{2.7}$$

To prove (2.6), we will first represent the jackknife pseudo-values into a sum of three components: marginal survival function, influence function of marginal survival, and the remaining term. Details will be given in Section 2.4.1. In Section 2.4.2, we will prove the consistency and asymptotic normality of the estimator defined by (2.6).

2.4.1 Asymptotic Unbiasedness

In this section we will prove the asymptotic unbiasedness property of the pseudo-values specified in (2.7). Let $T_{11}, T_{21}, \ldots, T_{n1}$ be a sample from the distribution P and the parameter of interest be $\psi(P(t)) = S_1(t)$, where $S_1(t)$ is the marginal survival function for the main event under the RSC. Suppose that we estimate $\psi(P(t))$ by $\psi(P_n(t))$, where $P_n(t)$ is the IPCW Kaplan-Meier estimator of $S_1(t)$ under the RSC, which is an empirical distribution of $S_1(t)$. Based on this specification, the jackknife pseudo-value for subject i at time t defined in (2.5) can be rewritten in the form specified as follows

$$J_{i,1}(t) = n\psi(P_n(t)) - (n-1)\psi(P_n^{-i}(t)),$$

where $P_n^{-i}(t)$ is the empirical distribution calculated from the reduced sample $T_{11}, T_{21}, \ldots, T_{i-1,1}, T_{i+1,1}, \ldots, T_{n1}$. Using the von Mises expansion of $\psi(P_n(t))$, we have

$$\psi(P_n) = \psi(P) + n^{-1}\sum_{i=1}^{n}\dot{\psi}(T_i) + \frac{1}{2}n^{-1}\sum_{i=1}^{n}\sum_{j=1}^{n}\ddot{\psi}(T_i, T_j) + O_P(n^{-\frac{3}{2}}), \tag{2.8}$$

where $\dot{\psi}$ and $\ddot{\psi}$ are the first- and second-order Gateaux derivatives of the functional ψ. Theorem 1 of Graw et al. (2009) proves that for a twice differentiable functional ψ with centered first derivatives, $E\{\dot{\psi}(X_i)\} = 0$, symmetric second derivatives, $\ddot{\psi}(X_i, X_j) = \ddot{\psi}(X_j, X_i)$, and $E\{\ddot{\psi}(X_i, y)\} = 0$ for all y, the jackknife pseudo-values can be represented by

$$n\psi(P_n) - (n-1)\psi(P_n^{(-i)}) = \psi(P) + \dot{\psi}(X_i) + o_P(1),$$

where $X_1, X_2, \ldots, X_n$ is a sample from the distribution P. Apply this theorem and the von Mises expansion (2.8), our jackknife pseudo-values for the IPCW Kaplan-Meier estimator can be expressed as the form

$$J_{i,1} = S_1(t) + \dot{\psi}(T_{i,1}) + o_P(1). \tag{2.9}$$

The first-order Gateaux derivatives of $\psi_1(P_n)$ is then given by

$$\dot{\psi}_1(T_{i,1}) = \frac{\delta_i F_1(t) - \tilde{N}_{i1}(t)}{G(\tilde{X}_i)} - \int_0^{\tilde{X}_i} \frac{P(T_i \le t, \epsilon_i = 1 | T_i \ge u) - F_1(t)}{G(u)} dM_G(u) + o_P(1), \tag{2.10}$$

where $F_1(t) = E\{N_{i1}(t)\} = 1 - S_1(t)$ is the marginal failure function of the main event, $dM_G(u) = I(\tilde{X}_i \in du, \delta_i = 0) - I(\tilde{X}_i \geq u)\Lambda_G(du)$ is the martingale; and $d\Lambda_G = -dG/G$ is the cumulative hazards function associated with $1 - G$.

Substitute (2.10) into (2.9), then take the expectation of the pseudo-values $J_{i1}(t)$ conditional on Z_i has the form

$$\begin{aligned} E\{J_{i,1}(t)|Z_i\} &= S_1(t) + F_1(t)\frac{E\{\delta_i|Z_i\}}{G(\tilde{X}_i)} - \frac{E\{I(\tilde{X}_i \leq t, \delta_i = 1, \epsilon_i = 1)|Z_i\}}{G(\tilde{X}_i)} + o_P(1) \\ &= S_1(t) + F_1(t) - F_1(t|Z_i) + o_P(1) \\ &= 1 - F_1(t|Z_i) + o_P(1) \\ &= S_1(t|Z_i) + o_P(1). \end{aligned}$$

This proves *asymptotic unbiasedness* (2.7).

2.4.2 Asymptotics of the GEE Estimator

Consistency and asymptotic normality of the solution of GEE (2.6) is investigated in this section. Analogous to Theorem 2 adopted from Graw et al. (2009), we have the following theorem:

Theorem 1. *Consider a time point t. Under mild regularity conditions regarding the link function $g(\cdot)$, the solution $\hat{\boldsymbol{\beta}}_{\boldsymbol{t,1}}$ to (2.6) is consistent and asymptotically normal for estimating the parameter $\boldsymbol{\beta}_{\boldsymbol{t,1}}$ of the model:*

$$\sqrt{n}(\hat{\boldsymbol{\beta}}_{\boldsymbol{t,1}} - \boldsymbol{\beta}_{\boldsymbol{t,1}}) \sim N(0, \Sigma_{t,1}),$$

where the asymptotic variance $\Sigma_{t,1}$ is consistently estimated by the sandwich-form:

$$\hat{\Sigma}_{t,1} = \hat{\Gamma}_{t,1}^{-1}(\hat{\boldsymbol{\beta}}_{\boldsymbol{t,1}}) Var\{U_{(n)}(\hat{\boldsymbol{\beta}}_{\boldsymbol{t,1}})\}\hat{\Gamma}_{t,1}^{-1}(\hat{\boldsymbol{\beta}}_{\boldsymbol{t,1}}),$$

where

$$\hat{\Gamma}_{t,1}(\hat{\boldsymbol{\beta}}_{\boldsymbol{t,1}}) = n^{-1}\sum_{i=1}^{n}\left\{\frac{\partial g^{-1}({\boldsymbol{\beta}_{\boldsymbol{t,1}}}^T \boldsymbol{Z_i})}{\partial \boldsymbol{\beta}_{\boldsymbol{t,1}}}\right\}^T V_{it,1}^{-1}\left\{\frac{\partial g^{-1}(\boldsymbol{\beta}_{\boldsymbol{t,1}}^{\boldsymbol{T}} \boldsymbol{Z_i})}{\partial \boldsymbol{\beta}_{\boldsymbol{t,1}}}\right\},$$

$$Var\Big\{U_{(n)}(\hat{\boldsymbol{\beta}}_{\boldsymbol{t,1}})\Big\} = n^{-1}\sum_{i=1}^{n} U_i(\hat{\boldsymbol{\beta}}_{\boldsymbol{t,1}})U_i^T(\hat{\boldsymbol{\beta}}_{\boldsymbol{t,1}}),$$

and $U_i(\cdot)$ *is denoted by (2.6) with* $U_n(\cdot) = \sum_i U_i(\cdot)$.

Proof. Consistency of the estimator can be shown by

$$E\{J_{i,1}(t) - g^{-1}(\beta_{t,1}^T Z_i)\} = 0.$$

To prove asymptotic normality, we will use the following two important properties when the jackknife pseudo-values $J_{i,1}(t)$ are represented by the form in (2.9):

1 $J_{i,1}(t)$ can be approximated by independently and identically distributed variables,

2 $E\{J_{i,1}(t)\} = S_1(t) + o_P(1), \forall i \in \{1, \ldots, n\}$.

Therefore, the score process can be approximated by a sum of independently and identically distributed random variables at the $n^{-1/2}$-rate:

$$U_{(n)}(\boldsymbol{\beta}_{\boldsymbol{t,1}}) = \sum_{i=1}^{n} \Big(\frac{\partial}{\partial \boldsymbol{\beta}_{\boldsymbol{t,1}}} g^{-1}(\boldsymbol{\beta}_{\boldsymbol{t,1}}^{\boldsymbol{T}} \boldsymbol{Z_i})\Big)^T V_{it,1}^{-1}\{\dot{\psi}_1(T_i) - g^{-1}(\boldsymbol{\beta}_{\boldsymbol{t,1}}^{\boldsymbol{T}} \boldsymbol{Z_i})\} + o_P(n^{-\frac{1}{2}}).$$

The rest of the proof is analogous to multivariate asymptotics of Theorem 2 of Liang and Zeger (1986). □

2.5 ESTIMATION AND INFERENCE ON MARGINAL SURVIVAL

Through pseudo-values for all subjects at all time points, the marginal survival probabilities for subject i at time t can be estimated by

$$\hat{S}_{i,1}(t|Z_{li}) = 1 - \exp[-\exp(\hat{\beta}_{0,1}(t) + \sum_{l=1}^{p} \hat{\beta}_{l,1} Z_{li})], \tag{2.11}$$

under the c-log-log link function and let

$$\hat{S}_{i,1}(t|Z_{li}) = g(\hat{\boldsymbol{\beta}})$$

where $\hat{\boldsymbol{\beta}} = (\hat{\beta}_{0,1}(t), \hat{\beta}_{1,1}, \ldots, \hat{\beta}_{p,1})$. $g : \Re^K \to \Re^L$, all the L entries of g have continuous partial derivatives with respect to $\boldsymbol{\beta}$ and given the properties of $\hat{\boldsymbol{\beta}}$ in Theorem 1.
Using delta method, we can show that

$$\sqrt{n}[g(\hat{\boldsymbol{\beta}}) - g(\boldsymbol{\beta})] \xrightarrow{d} N(0, G\Sigma G^T)$$

where Σ can be obtained from the sandwich covariance estimates of $\hat{\boldsymbol{\beta}}$ and

$$G = \bigtriangledown g(\boldsymbol{\beta}) = (\frac{\partial S_{i,1}(t|Z_{li})}{\partial \beta_0(t)}, \frac{\partial S_{i,1}(t|Z_{li})}{\partial \beta_1}, \ldots, \frac{\partial S_{i,1}(t|Z_{li})}{\partial \beta_p})$$

where

$$\frac{\partial S_{i,1}(t|Z_{li})}{\partial \beta_{0,1}(t)} = \exp[\beta_{0,1}(t) + \sum_{l=1}^{p} \beta_{l,1} Z_{li} - \exp\{\beta_{0,1}(t) + \sum_{l=1}^{p} \beta_{l,1} Z_{li}\}],$$

$$\frac{\partial S_{i,1}(t|Z_{li})}{\partial \beta_{l,1}} = Z_{li} \exp[\beta_{0,1}(t) + \sum_{l=1}^{p} \beta_{l,1} Z_{li} - \exp\{\beta_{0,1}(t) + \sum_{l=1}^{p} \beta_{l,1} Z_{li}\}], l = 1, \ldots, p.$$

$\hat{G}$ can be estimated by evaluating the above partial derivatives at $\boldsymbol{\beta} = \hat{\boldsymbol{\beta}}$.
Thus, the covariance of $\hat{S}_{i,1}(t|Z_{li})$ can be estimated by $\frac{1}{n}\hat{G}\hat{\Sigma}\hat{G}^T$ and we can make inference on survival for everyone at any time point.

3.0 SIMULATION STUDIES

In this section, we conduct numerical analyses to assess the performance of our proposed estimators, the estimated covariate effects and the estimated marginal survival defined by (2.6) and (2.11), respectively. We simulate scenarios under different competing risks and censoring proportions for small to moderate sample sizes.

There were two covariates $Z_i = (Z_{i1}, Z_{i2})$, which were independent and identically distributed standard normal variates and Bernoulli(0.6) variates, respectively. The Cox proportional hazards function for type 1 failure (the main event) were given by

$$\lambda_1(T_1|\boldsymbol{Z}) = \lambda_{10}(t)\exp(\beta \boldsymbol{Z}^T),$$

where we assumed an exponential baseline hazards of $\lambda_{10}(t) = 1$, a Weibull baseline hazards of $\lambda_{10}(t) = \lambda\nu t^{\nu-1}$ (the scale parameter λ was set to be 2 and the shape parameter ν was set to be 1.5), and a Gompertz baseline hazard of $\lambda_{10}(t) = \eta\exp(\alpha t)$ (the scale parameter η was set to be 1.5 and the shape parameter α was set to be 0.5), respectively.

Under the RSC assumption, type 2 failure (the competing event) times were obtained by taking $T_2 = T_1 - (1-2\epsilon)V$, where V followed a uniform distribution $Unif(0, T_1)$ and a random variable ϵ was generated from a logistic model given by $E(\epsilon) = \{1 + \exp(-\gamma)\}^{-1}$, where the parameter $\gamma \in (-\infty, \infty)$. The true parameter values were $(\beta_1, \beta_2) = (1, 1)$. Censoring times were independently generated from an exponential distribution with rate λ_c. Different γ and λ_c were chosen to produce varying amounts of competing events and censoring.

Data with sample sizes of $n = 300$ or 600 were generated. To evaluate our proposed estimator defined by (2.6), we calculated the relative percent bias (RPB), average of the standard error of estimates (SE), standard deviation of the estimates (SD), and empirical coverage probability (CP) of the sample 95% confidence intervals based on 1000 simulated

datasets. For comparison, we evaluated the proposed estimator (RSC-Pseudo) together with those of the original random signs censoring model (RSC) proposed by Yabes in 2012 and the Cox proportional hazards model (Cox). In addition, we evaluated the estimator of marginal survival defined by (2.11) by calculating the relative percent bias of survival (RPBS) at the 25th, 50th, and 75th percentiles of the type 1 failure times.

Tables 3.1 and 3.2 show simulation results of the estimated covariate effects where the main event times were generated with exponential baseline hazards for sample sizes of 300 and 600, respectively. The results show that, with 80% of type 1 failure, the RPB of the estimators are small and the coverage probability is close to the nominal level for both RSC-Pseudo and RSC models. The overall performance of the Cox model is acceptable. As the level of type 1 failure decreases to 30%, the RPBs become larger but still less than 6% for RSC family models (RSC-Pseudo and RSC). However, the estimators for the Cox model are severely biased with RPB fell in between 11% and 18% and coverage probability as low as 78%. With sample sizes of 600, performance of the estimators significantly improve for RSC family models. For the Cox model, the RPBs remain in the same range and coverage probability gets lower as the sample sizes increase to 600. Overall, for moderate or low level of type 1 failures (50% or 30%), the performance of the models are affected by both proportions of competing events and censoring, the RPB gets larger as the type 2 failure or censoring cases increase. The performance of the Cox model is extremely sensitive to the proportion of type 2 failure.

In Table 3.3, we report the risk prediction performance of the marginal survival estimate. The RPBS gets larger towards the end of the time course and as the proportion of type 2 failure gets higher. In general, the RPBS is less than 2% at the 25th percentile, less than 4% at the 50th percentile, and less than 8% at the 75th percentile of type 1 failure times, even with a small sample size of 300.

Simulation results of the estimated covariate effects where the main event times were generated with Weibull baseline hazards are shown in table 3.4 and 3.5 for sample sizes of 300 and 600, respectively. The RPBs are less than 7% for the RSC family models with sample size of 300 and get smaller ($\leq 6\%$) with sample size of 600; average of the standard error of estimates are close to the standard deviation of the estimates, the desired coverage

(95%) was maintained very well. The performance of the estimators are affected by both the proportions of censoring and type 2 failure, and mainly depends on the amount of type 1 failures. While, for the Cox model, the range of the RPBs are from 10% to 20% when the proportion of type 2 failure is relative high and the coverage probability is far below 95%. The RPBs of the RSC models are slightly smaller than those of the RSC-Pseudo models, one explanation could be that RSC-Pseudo model was derived using approximation method (asymptotic unbiasedness of Pseudo-values) rather than an exact partial likelihood based RSC model. However, it is also noticeable that the coverage probabilities of the RSC-Pseudo models maintain very well, above 90% with 30% of type 1 failure and sample size of 300 and around 95% when the sample size increases to 600. The nice property may be attributable to the better 'recovery' of censoring information by Pseudo-values approach.

Tables 3.7 and 3.8 show simulation results of the Gompertz baseline hazards with sample sizes of 300 and 600, respectively. The performance of the estimators are similar to those of Weibull baseline hazards distribution discussed above.

Tables 3.6 and 3.9 show simulation results of risk prediction using the Weibull baseline hazards distribution and Gompertz baseline hazards distribution, respectively. The performance of the estimators are similar to those of the exponential baseline hazards distribution reported in table 3.3.

One scenario where RSC assumption violated was setup as follows: two covariates $Z_i = (Z_{i1}, Z_{i2})$ were generated from standard normal variates and Bernoulli(0.6) variates, respectively. The true parameter values were $(\beta_1, \beta_2) = (1, 1)$. p is the proportion of failure type 1. Type 1 failure times were generated from the subdistributions:

$$Pr(T_i \leq t, \epsilon_i = 1 | \boldsymbol{Z_i}) = 1 - [1 - p\{1 - \exp(-t)\}]^{\exp(\boldsymbol{Z_i}\beta_1)},$$

which is a unit exponential mixture with mass $1 - p$ at ∞ when $\boldsymbol{Z_i} = (0, 0)$. The subdistribution for type 2 failures was then obtained by taking $Pr(T_i \leq t | \epsilon_i = 2, \boldsymbol{Z_i}) = 1 - \exp(-t)^{\exp(\boldsymbol{Z_i}\beta_2)}$. Censoring times were independently generated from an exponential distribution with rate λ_c.Under this setting, two competing risks are negatively correlated, an opposite to RSC assumption. Simulation results are shown in table 10.

Table 3.1: Simulation results: type 1 failure time generated from exponential baseline hazard (n=300)

				RSC-Pseudo				RSC				Cox			
λ_c	γ	$(\%T_1, \%T_2, \%C)$		RPB	SE	SD	CP	RPB	SE	SD	CP	RPB	SE	SD	CP
0	1.40	$(80, 20, 0)$	β_1	1.1	0.170	0.175	0.950	0.3	0.143	0.148	0.945	3.8	0.146	0.148	0.939
			β_2	1.6	0.100	0.102	0.942	0.7	0.084	0.085	0.950	4.1	0.086	0.087	0.937
0.10	1.90	$(80, 13, 7)$	β_1	0.8	0.186	0.190	0.950	0.2	0.154	0.157	0.940	2.3	0.145	0.147	0.950
			β_2	0.5	0.115	0.104	0.965	0.4	0.088	0.088	0.947	2.1	0.085	0.085	0.943
0.20	2.50	$(80, 7, 13)$	β_1	0.3	0.206	0.203	0.944	0.2	0.165	0.177	0.934	2.0	0.145	0.146	0.954
			β_2	0.6	0.130	0.112	0.967	0.8	0.093	0.092	0.944	1.8	0.085	0.086	0.945
0	0	$(50, 50, 0)$	β_1	2.1	0.214	0.240	0.922	1.2	0.182	0.196	0.933	11.4	0.186	0.189	0.914
			β_2	2.3	0.126	0.133	0.942	1.4	0.107	0.113	0.943	11.9	0.111	0.111	0.825
0.35	0.55	$(50, 33, 17)$	β_1	1.1	0.308	0.299	0.946	< 0.01	0.235	0.262	0.908	6.7	0.184	0.182	0.949
			β_2	0.5	0.191	0.169	0.940	< 0.01	0.126	0.136	0.929	7.8	0.107	0.110	0.894
0.90	1.30	$(50, 17, 33)$	β_1	7.7	0.402	0.417	0.893	6.8	0.290	0.365	0.855	4.5	0.185	0.190	0.943
			β_2	7.4	0.227	0.216	0.828	5.5	0.144	0.170	0.872	4.7	0.104	0.103	0.936
0	-0.85	$(30, 70, 0)$	β_1	3.8	0.273	0.306	0.929	1.5	0.238	0.257	0.935	18.1	0.243	0.247	0.935
			β_2	4.4	0.162	0.190	0.910	1.9	0.140	0.156	0.933	18.1	0.146	0.150	0.780
0.22	-0.60	$(30, 60, 10)$	β_1	5.0	0.383	0.388	0.946	5.4	0.288	0.330	0.907	16.2	0.240	0.250	0.909
			β_2	5.7	0.241	0.228	0.937	6.1	0.159	0.173	0.915	16.6	0.142	0.143	0.799
0.54	-0.37	$(30, 50, 20)$	β_1	1.4	0.491	0.521	0.919	2.3	0.338	0.413	0.878	14.1	0.242	0.238	0.926
			β_2	2.0	0.295	0.291	0.892	2.1	0.178	0.203	0.910	13.8	0.139	0.141	0.832
0.97	-0.09	$(30, 40, 30)$	β_1	1.2	0.627	0.688	0.893	1.1	0.379	0.522	0.821	11.5	0.243	0.246	0.930
			β_2	4.7	0.338	0.403	0.822	3.6	0.190	0.237	0.866	12.0	0.137	0.137	0.883

RSC-Pseudo: the proposed model; RSC: the original random signs censoring model; Cox: the Cox proportional hazards model;
RPB: Relative Percent Bias; SE: average of the standard error estimates; SD: empirical standard deviation;
CP: empirical coverage probability(95%); T_1: main event; T_2: competing event; C: censoring;
$\boldsymbol{\beta} = (1, 1)$; $\beta_1 : \boldsymbol{Z_1} \sim B(1, 0.6)$; $\beta_2 : \boldsymbol{Z_2} \sim N(0, 1)$

Table 3.2: Simulation results: type 1 failure time generated from exponential baseline hazard (n=600)

				RSC-Pseudo				RSC				Cox			
λ_c	γ	$(\%T_1, \%T_2, \%C)$		RPB	SE	SD	CP	RPB	SE	SD	CP	RPB	SE	SD	CP
0	1.40	$(80, 20, 0)$	β_1	0.8	0.121	0.124	0.950	0.3	0.101	0.100	0.953	3.7	0.102	0.101	0.942
			β_2	0.9	0.071	0.071	0.951	0.6	0.060	0.062	0.944	4.1	0.061	0.061	0.908
0.10	1.90	$(80, 13, 7)$	β_1	0.1	0.133	0.130	0.953	0.1	0.110	0.115	0.934	2.2	0.102	0.104	0.942
			β_2	0.4	0.083	0.073	0.968	0.2	0.063	0.063	0.943	2.6	0.060	0.060	0.936
0.20	2.50	$(80, 7, 13)$	β_1	0.2	0.149	0.139	0.964	0.2	0.121	0.125	0.938	1.6	0.102	0.101	0.955
			β_2	1.1	0.095	0.079	0.964	0.6	0.067	0.068	0.940	1.6	0.059	0.059	0.950
0	0	$(50, 50, 0)$	β_1	1.8	0.153	0.153	0.949	1.2	0.129	0.127	0.946	11.5	0.130	0.128	0.867
			β_2	1.6	0.090	0.092	0.948	0.9	0.076	0.078	0.937	11.5	0.077	0.077	0.701
0.35	0.55	$(50, 33, 17)$	β_1	0.4	0.231	0.213	0.952	1.8	0.178	0.196	0.923	8.0	0.129	0.126	0.906
			β_2	0.8	0.147	0.118	0.956	< 0.01	0.094	0.097	0.933	7.3	0.074	0.076	0.845
0.90	1.30	$(50, 17, 33)$	β_1	8.7	0.313	0.316	0.899	6.6	0.231	0.294	0.850	4.5	0.130	0.124	0.952
			β_2	6.8	0.187	0.161	0.830	4.9	0.115	0.126	0.881	4.0	0.072	0.070	0.931
0	-0.85	$(30, 70, 0)$	β_1	1.7	0.196	0.209	0.935	1.0	0.167	0.169	0.962	18.1	0.169	0.170	0.828
			β_2	1.8	0.115	0.119	0.929	0.7	0.097	0.098	0.946	17.9	0.101	0.103	0.606
0.22	-0.60	$(30, 60, 10)$	β_1	4.5	0.281	0.275	0.957	5.9	0.231	0.249	0.900	15.6	0.168	0.169	0.851
			β_2	3.8	0.181	0.145	0.969	4.5	0.115	0.116	0.934	15.0	0.098	0.094	0.698
0.54	-0.37	$(30, 50, 20)$	β_1	2.6	0.376	0.363	0.949	3.3	0.265	0.319	0.890	13.5	0.169	0.173	0.878
			β_2	2.3	0.232	0.198	0.922	2.5	0.134	0.155	0.910	13.6	0.097	0.098	0.715
0.97	-0.09	$(30, 40, 30)$	β_1	2.7	0.454	0.479	0.898	1.9	0.303	0.420	0.824	11.7	0.169	0.174	0.890
			β_2	3.3	0.256	0.243	0.846	2.2	0.147	0.184	0.869	11.5	0.095	0.092	0.797

RSC-Pseudo: the proposed model; RSC: the original random signs censoring model; Cox: the Cox proportional hazards model;
RPB: Relative Percent Bias; SE: average of the standard error estimates; SD: empirical standard deviation;
CP: empirical coverage probability(95%); T_1: main event; T_2: competing event; C: censoring;
$\boldsymbol{\beta} = (1, 1)$; $\beta_1 : \boldsymbol{Z_1} \sim B(1, 0.6)$; $\beta_2 : \boldsymbol{Z_2} \sim N(0, 1)$

Table 3.3: Simulation results: risk prediction for type 1 failure time generated from exponential baseline hazard.

			n=300			n=600		
λ_c	γ	$(\%T_1, \%T_2, \%C)$	RPBS(T_25%)	RPBS(T_50%)	RPBS(T_75%)	RPBS(T_25%)	RPBS(T_50%)	RPBS(T_75%)
0	1.40	$(80, 20, 0)$	0.37	0.42	1.20	0.18	0.12	0.40
0.09	1.90	$(80, 13, 7)$	0.19	0.41	1.18	0.25	0.47	0.54
0.19	2.50	$(80, 7, 13)$	0.12	0.15	0.49	0.16	0.17	0.45
0	0	$(50, 50, 0)$	0.60	1.21	2.18	0.39	0.98	1.71
0.35	0.55	$(50, 33, 17)$	0.88	1.36	1.78	0.51	1.05	2.06
0.90	1.30	$(50, 17, 33)$	0.49	1.31	3.01	0.43	0.75	2.61
0	-0.85	$(30, 70, 0)$	0.86	1.98	4.09	0.39	0.60	1.87
0.22	-0.60	$(30, 60, 10)$	2.01	3.89	7.84	1.58	3.28	7.45
0.54	-0.37	$(30, 50, 20)$	1.15	2.67	4.37	1.53	3.29	5.41
0.97	-0.09	$(30, 40, 30)$	0.18	0.62	0.53	0.53	1.28	1.51

RPBS: Relative Percent Bias of Survival; T_25%: Time at 25th percentile; T_50%: Time at 50th percentile; T_75%: Time at 75th percentile.

Table 3.4: Simulation results: type1 failure time generated from Weibulll baseline hazard (n=300)

				RSC-Pseudo				RSC				Cox			
λ_c	γ	$(\%T_1, \%T_2, \%C)$		RPB	SE	SD	CP	RPB	SE	SD	CP	RPB	SE	SD	CP
0	1.40	$(80, 20, 0)$	β_1	1.2	0.170	0.181	0.930	0.7	0.144	0.148	0.935	4.3	0.146	0.147	0.942
			β_2	1.3	0.100	0.104	0.942	0.6	0.084	0.088	0.932	3.9	0.087	0.088	0.933
0.17	1.80	$(80, 13, 7)$	β_1	0.6	0.182	0.185	0.947	< 0.01	0.151	0.153	0.946	2.4	0.146	0.149	0.946
			β_2	1.4	0.111	0.110	0.949	0.7	0.087	0.090	0.940	3.1	0.086	0.089	0.927
0.32	2.60	$(80, 7, 13)$	β_1	1.2	0.190	0.200	0.937	1.1	0.155	0.164	0.937	2.2	0.145	0.151	0.939
			β_2	0.8	0.117	0.105	0.976	0.2	0.088	0.090	0.939	1.6	0.085	0.085	0.951
0	0	$(50, 50, 0)$	β_1	1.0	0.214	0.227	0.938	0.3	0.183	0.186	0.945	10.8	0.186	0.188	0.914
			β_2	2.1	0.126	0.137	0.936	0.8	0.107	0.116	0.923	11.1	0.111	0.113	0.846
0.52	0.52	$(50, 33, 17)$	β_1	1.2	0.271	0.265	0.940	0.4	0.213	0.226	0.940	6.6	0.185	0.175	0.950
			β_2	4.4	0.171	0.156	0.980	3.6	0.119	0.127	0.930	9.3	0.108	0.114	0.860
1.20	1.26	$(50, 17, 33)$	β_1	0.4	0.444	0.329	0.941	0.1	0.252	0.298	0.905	4.6	0.186	0.189	0.942
			β_2	1.3	0.204	0.200	0.937	0.6	0.131	0.141	0.913	5.1	0.105	0.107	0.934
0	-0.85	$(30, 70, 0)$	β_1	4.2	0.274	0.312	0.922	1.2	0.239	0.265	0.926	19.1	0.244	0.251	0.892
			β_2	4.5	0.163	0.185	0.918	2.0	0.141	0.155	0.933	19.5	0.146	0.150	0.751
0.35	-0.60	$(30, 60, 10)$	β_1	7.1	0.339	0.358	0.955	6.2	0.268	0.301	0.923	17.6	0.242	0.244	0.898
			β_2	7.0	0.215	0.207	0.957	5.4	0.151	0.164	0.917	16.8	0.142	0.143	0.803
0.80	-0.33	$(30, 50, 20)$	β_1	5.2	0.402	0.410	0.946	5.0	0.302	0.339	0.911	15.2	0.241	0.242	0.921
			β_2	4.1	0.247	0.244	0.937	3.6	0.162	0.190	0.891	13.7	0.139	0.142	0.850
1.30	0	$(30, 40, 30)$	β_1	3.1	0.482	0.517	0.915	2.4	0.331	0.419	0.874	11.2	0.239	0.251	0.930
			β_2	4.0	0.298	0.296	0.935	3.6	0.173	0.193	0.927	12.4	0.136	0.137	0.865

RSC-Pseudo: the proposed model; RSC: the original random signs censoring model; Cox: the Cox proportional hazards model;
RPB: Relative Percent Bias; SE: average of the standard error estimates; SD: empirical standard deviation;
CP: empirical coverage probability(95%); T_1: main event; T_2: competing event; C: censoring;
$\boldsymbol{\beta} = (1, 1)$; $\beta_1 : \boldsymbol{Z_1} \sim B(1, 0.6)$; $\beta_2 : \boldsymbol{Z_2} \sim N(0, 1)$

Table 3.5: Simulation results: type 1 failure time from Weibulll baseline hazard (n=600)

				RSC-Pseudo				RSC				Cox			
λ_c	γ	$(\%T_1, \%T_2, \%C)$		RPB	SE	SD	CP	RPB	SE	SD	CP	RPB	SE	SD	CP
0	1.40	$(80, 20, 0)$	β_1	1.1	0.121	0.125	0.938	0.8	0.101	0.103	0.946	4.2	0.102	0.101	0.932
			β_2	0.4	0.071	0.075	0.937	< 0.01	0.060	0.063	0.933	3.3	0.060	0.062	0.920
0.17	1.80	$(80, 13, 7)$	β_1	0.6	0.129	0.129	0.946	0.1	0.107	0.110	0.938	2.4	0.103	0.105	0.937
			β_2	1.0	0.079	0.076	0.953	0.6	0.062	0.064	0.946	2.8	0.060	0.063	0.924
0.32	2.60	$(80, 7, 13)$	β_1	0.2	0.135	0.125	0.962	0.2	0.111	0.108	0.960	1.6	0.102	0.097	0.955
			β_2	0.1	0.084	0.076	0.970	0.2	0.063	0.064	0.938	1.2	0.059	0.061	0.939
0	0	$(50, 50, 0)$	β_1	1.7	0.153	0.160	0.947	1.0	0.129	0.134	0.944	11.6	0.130	0.134	0.851
			β_2	1.7	0.090	0.094	0.936	1.0	0.076	0.079	0.937	11.4	0.077	0.079	0.692
0.52	0.52	$(50, 33, 17)$	β_1	2.3	0.191	0.182	0.962	2.4	0.152	0.164	0.935	7.8	0.129	0.131	0.908
			β_2	1.5	0.121	0.098	0.989	1.5	0.084	0.082	0.959	7.6	0.075	0.073	0.853
1.20	1.26	$(50, 17, 33)$	β_1	0.6	0.244	0.234	0.948	0.6	0.188	0.209	0.908	4.5	0.130	0.130	0.942
			β_2	0.6	0.153	0.129	0.967	0.1	0.098	0.099	0.940	4.5	0.074	0.073	0.916
0	-0.85	$(30, 70, 0)$	β_1	2.1	0.197	0.206	0.947	0.8	0.167	0.174	0.946	18.7	0.170	0.171	0.811
			β_2	2.4	0.116	0.116	0.956	1.0	0.098	0.096	0.960	18.8	0.101	0.099	0.555
0.35	-0.60	$(30, 60, 10)$	β_1	6.1	0.242	0.243	0.949	5.9	0.190	0.200	0.926	16.8	0.168	0.168	0.843
			β_2	5.2	0.153	0.131	0.979	4.5	0.106	0.111	0.922	16.3	0.098	0.101	0.635
0.80	-0.33	$(30, 50, 20)$	β_1	4.2	0.312	0.306	0.955	3.7	0.222	0.259	0.895	13.4	0.168	0.169	0.892
			β_2	5.3	0.190	0.171	0.967	4.9	0.120	0.128	0.921	13.8	0.096	0.099	0.716
1.30	0	$(30, 40, 30)$	β_1	4.6	0.346	0.348	0.952	4.5	0.252	0.297	0.880	10.4	0.166	0.170	0.904
			β_2	2.0	0.213	0.201	0.955	1.9	0.130	0.144	0.912	10.4	0.094	0.095	0.816

RSC-Pseudo: the proposed model; RSC: the original random signs censoring model; Cox: the Cox proportional hazards model;
RPB: Relative Percent Bias; SE: average of the standard error estimates; SD: empirical standard deviation;
CP: empirical coverage probability(95%); T_1: main event; T_2: competing event; C: censoring;
$\boldsymbol{\beta} = (1, 1)$; $\beta_1 : \boldsymbol{Z_1} \sim B(1, 0.6)$; $\beta_2 : \boldsymbol{Z_2} \sim N(0, 1)$

Table 3.6: Simulation results: risk prediction for type 1 failure time generated from Weibulll baseline hazard.

			n=300			n=600		
λ_c	γ	$(\%T_1, \%T_2, \%C)$	RPBS(T_25%)	RPBS(T_50%)	RPBS(T_75%)	RPBS(T_25%)	RPBS(T_50%)	RPBS(T_75%)
0	1.40	$(80, 20, 0)$	0.63	0.77	1.43	0.25	0.30	0.75
0.17	1.80	$(80, 13, 7)$	0.52	0.99	1.57	0.18	0.64	1.25
0.32	2.60	$(80, 7, 13)$	0.59	0.91	1.33	0.13	0.32	0.60
0	0	$(50, 50, 0)$	0.92	1.19	2.14	0.52	0.82	1.00
0.52	0.52	$(50, 33, 17)$	0.47	1.54	3.88	0.83	1.58	2.75
1.20	1.26	$(50, 17, 33)$	0.13	0.43	1.35	0.35	0.74	1.25
0	-0.85	$(30, 70, 0)$	1.04	2.82	4.64	0.27	0.60	1.97
0.35	-0.60	$(30, 60, 10)$	1.91	3.57	6.63	1.53	2.86	5.86
0.80	-0.33	$(30, 50, 20)$	1.09	2.75	6.36	1.12	2.95	6.05
1.30	0	$(30, 40, 30)$	0.46	1.94	4.75	0.46	1.76	4.09

RPBS: Relative Percent Bias of Survival; T_25%: Time at 25th percentile; T_50%: Time at 50th percentile; T_75%: Time at 75th percentile.

Table 3.7: Simulation results: type 1 failure time generated from Gompertz baseline hazard (n=300)

				RSC-Pseudo				RSC				Cox			
λ_c	γ	$(\%T_1, \%T_2, \%C)$		RPB	SE	SD	CP	RPB	SE	SD	CP	RPB	SE	SD	CP
0	1.40	$(80, 20, 0)$	β_1	1.1	0.170	0.181	0.938	0.7	0.144	0.148	0.948	3.7	0.146	0.147	0.944
			β_2	1.6	0.100	0.103	0.944	0.7	0.084	0.087	0.943	4.0	0.087	0.088	0.932
0.18	1.85	$(80, 13, 7)$	β_1	1.1	0.183	0.182	0.946	0.7	0.151	0.152	0.943	3.0	0.145	0.144	0.953
			β_2	1.7	0.111	0.105	0.965	1.3	0.087	0.088	0.939	3.4	0.086	0.087	0.938
0.37	2.57	$(80, 7, 13)$	β_1	1.0	0.197	0.200	0.946	0.5	0.160	0.171	0.936	1.6	0.145	0.149	0.941
			β_2	0.7	0.123	0.110	0.968	0.6	0.090	0.093	0.954	1.8	0.085	0.087	0.947
0	0	$(50, 50, 0)$	β_1	3.0	0.215	0.228	0.933	1.3	0.183	0.191	0.947	10.9	0.186	0.189	0.920
			β_2	2.7	0.126	0.139	0.930	1.1	0.107	0.117	0.921	11.0	0.111	0.116	0.849
0.60	0.50	$(50, 33, 17)$	β_1	4.2	0.287	0.286	0.947	3.0	0.223	0.250	0.917	8.2	0.185	0.191	0.927
			β_2	3.9	0.183	0.153	0.974	2.7	0.122	0.127	0.938	8.0	0.108	0.110	0.892
1.55	1.30	$(50, 17, 33)$	β_1	3.9	0.387	0.386	0.921	3.4	0.282	0.347	0.874	3.5	0.186	0.187	0.940
			β_2	2.0	0.232	0.199	0.913	1.8	0.143	0.155	0.919	4.9	0.105	0.103	0.943
0	-0.85	$(30, 70, 0)$	β_1	4.3	0.273	0.302	0.930	2.5	0.239	0.258	0.924	19.1	0.244	0.252	0.896
			β_2	3.8	0.162	0.186	0.919	1.4	0.139	0.155	0.922	17.1	0.145	0.151	0.801
0.40	-0.65	$(30, 60, 10)$	β_1	9.2	0.365	0.366	0.957	7.6	0.282	0.305	0.931	16.4	0.245	0.242	0.909
			β_2	9.3	0.233	0.210	0.970	7.0	0.156	0.169	0.912	16.7	0.144	0.148	0.797
1.00	-0.37	$(30, 50, 20)$	β_1	9.9	0.477	0.456	0.955	7.3	0.335	0.397	0.894	15.6	0.245	0.244	0.925
			β_2	8.4	0.301	0.268	0.943	5.2	0.177	0.201	0.900	13.8	0.140	0.140	0.859
1.66	-0.06	$(30, 40, 30)$	β_1	5.5	0.577	0.628	0.913	2.9	0.372	0.518	0.833	12.2	0.242	0.251	0.931
			β_2	5.2	0.343	0.301	0.916	2.0	0.188	0.224	0.907	11.3	0.135	0.133	0.889

RSC-Pseudo: the proposed model; RSC: the original random signs censoring model; Cox: the Cox proportional hazards model;
RPB: Relative Percent Bias; SE: average of the standard error estimates; SD: empirical standard deviation;
CP: empirical coverage probability(95%); T_1: main event; T_2: competing event; C: censoring;
$\boldsymbol{\beta} = (1, 1)$; $\beta_1 : \boldsymbol{Z_1} \sim B(1, 0.6)$; $\beta_2 : \boldsymbol{Z_2} \sim N(0, 1)$

Table 3.8: Simulation results: type 1 failure time generated from Gompertz baseline hazard (n=600)

				RSC-Pseudo				RSC				Cox			
λ_c	γ	$(\%T_1, \%T_2, \%C)$		RPB	SE	SD	CP	RPB	SE	SD	CP	RPB	SE	SD	CP
0	1.40	$(80, 20, 0)$	β_1	0.6	0.121	0.125	0.946	0.2	0.101	0.108	0.930	3.3	0.102	0.108	0.921
			β_2	0.7	0.071	0.072	0.942	0.3	0.060	0.061	0.938	3.6	0.060	0.061	0.938
0.18	1.85	$(80, 13, 7)$	β_1	1.4	0.130	0.134	0.943	1.1	0.107	0.111	0.940	3.0	0.102	0.102	0.947
			β_2	0.6	0.079	0.071	0.971	0.3	0.061	0.059	0.955	2.3	0.060	0.057	0.948
0.37	2.57	$(80, 7, 13)$	β_1	0.8	0.140	0.135	0.960	0.7	0.114	0.118	0.947	1.4	0.102	0.102	0.949
			β_2	0.7	0.087	0.075	0.972	0.5	0.064	0.064	0.945	1.6	0.059	0.060	0.944
0	0	$(50, 50, 0)$	β_1	0.7	0.153	0.157	0.942	< 0.01	0.129	0.131	0.943	10.5	0.130	0.128	0.888
			β_2	1.0	0.090	0.094	0.937	0.4	0.075	0.079	0.937	10.2	0.077	0.077	0.755
0.60	0.50	$(50, 33, 17)$	β_1	2.7	0.206	0.191	0.963	2.2	0.163	0.176	0.923	7.5	0.130	0.132	0.909
			β_2	2.2	0.132	0.104	0.979	2.2	0.089	0.090	0.940	7.5	0.075	0.074	0.841
1.55	1.30	$(50, 17, 33)$	β_1	0.9	0.294	0.278	0.935	0.9	0.218	0.262	0.876	4.1	0.130	0.137	0.932
			β_2	2.0	0.179	0.147	0.925	1.9	0.109	0.121	0.906	4.0	0.073	0.072	0.924
0	-0.85	$(30, 70, 0)$	β_1	2.3	0.196	0.209	0.935	1.4	0.167	0.170	0.928	17.6	0.169	0.169	0.839
			β_2	2.1	0.116	0.124	0.927	1.0	0.098	0.101	0.937	17.1	0.101	0.104	0.612
0.40	-0.65	$(30, 60, 10)$	β_1	7.2	0.258	0.249	0.959	6.0	0.202	0.219	0.932	15.4	0.170	0.170	0.863
			β_2	6.8	0.166	0.135	0.979	5.8	0.112	0.116	0.918	15.2	0.099	0.096	0.697
1.00	-0.37	$(30, 50, 20)$	β_1	7.5	0.353	0.323	0.964	7.0	0.256	0.300	0.896	13.0	0.170	0.168	0.887
			β_2	7.5	0.224	0.178	0.968	5.8	0.132	0.145	0.914	13.1	0.097	0.097	0.755
1.66	-0.06	$(30, 40, 30)$	β_1	3.3	0.422	0.424	0.933	2.6	0.292	0.372	0.858	10.9	0.168	0.166	0.914
			β_2	3.8	0.264	0.232	0.919	2.5	0.147	0.178	0.895	10.6	0.094	0.098	0.808

RSC-Pseudo: the proposed model; RSC: the original random signs censoring model; Cox: the Cox proportional hazards model;
RPB: Relative Percent Bias; SE: average of the standard error estimates; SD: empirical standard deviation;
CP: empirical coverage probability(95%); T_1: main event; T_2: competing event; C: censoring;
$\boldsymbol{\beta} = (1, 1)$; $\beta_1 : \boldsymbol{Z_1} \sim B(1, 0.6)$; $\beta_2 : \boldsymbol{Z_2} \sim N(0, 1)$

Table 3.9: Simulation results: risk prediction for type 1 failure time generated from Gompertz baseline hazard.

			n=300			n=600		
λ_c	γ	$(\%T_1, \%T_2, \%C)$	RPBS(T_25%)	RPBS(T_50%)	RPBS(T_75%)	RPBS(T_25%)	RPBS(T_50%)	RPBS(T_75%)
0	1.40	$(80, 20, 0)$	0.40	0.58	1.39	0.22	0.39	0.51
0.18	1.85	$(80, 13, 7)$	0.41	0.55	1.29	0.32	0.51	1.03
0.37	2.57	$(80, 7, 13)$	0.46	0.69	1.71	0.31	0.57	0.84
0	0	$(50, 50, 0)$	0.70	1.27	2.14	0.47	0.92	1.23
0.60	0.50	$(50, 33, 17)$	0.99	2.17	4.44	0.90	1.95	3.51
1.55	1.30	$(50, 17, 33)$	0.26	0.29	0.36	0.21	0.41	0.17
0	-0.85	$(30, 70, 0)$	1.38	1.70	4.05	0.45	0.58	1.33
0.40	-0.65	$(30, 60, 10)$	2.49	4.99	9.87	1.80	4.12	8.14
1.00	-0.37	$(30, 50, 20)$	2.07	4.68	8.51	2.02	4.33	8.74
1.66	-0.06	$(30, 40, 30)$	1.64	3.03	5.45	1.46	3.42	5.78

RPBS: Relative Percent Bias of Survival; T_25%: Time at 25th percentile; T_50%: Time at 50th percentile; T_75%: Time at 75th percentile.

Table 3.10: Simulation results: Violation of RSC (n=600)

				RSC-Pseudo				RSC				Cox			
λ_c	p	$(\%T_1, \%T_2, \%C)$		RPB	SE	SD	CP	RPB	SE	SD	CP	RPB	SE	SD	CP
0	0.80	$(84, 16, 0)$	β_1	22.1	0.118	0.122	0.532	27.1	0.102	0.106	0.263	1.9	0.098	0.101	0.940
			β_2	20.7	0.066	0.066	0.137	25.0	0.059	0.059	0.013	1.8	0.056	0.058	0.924
1.00	0.80	$(55, 5, 40)$	β_1	30.4	0.299	0.319	0.697	24.8	0.250	0.329	0.700	2.9	0.124	0.130	0.918
			β_2	27.6	0.143	0.155	0.395	22.7	0.116	0.145	0.464	2.5	0.067	0.068	0.928

RSC-Pseudo: the proposed model; RSC: the original randome signs censoring model; Cox: the Cox proportional hazards model;
RPB: Relative Percent Bias; SE: average of the standard error estimates; SD: empirical standard deviation;
CP: empirical coverage probability(95%); T_1: main event; T_2: competing event; C: censoring;
$\boldsymbol{\beta} = (1, 1)$; $\beta_1 : \boldsymbol{Z_1} \sim B(1, 0.6)$; $\beta_2 : \boldsymbol{Z_2} \sim N(0, 1)$

4.0 APPLICATIONS

Liver donations to patients with end-stage liver disease in the United States are managed and allocated by the United Network for Organ Sharing (UNOS). One of the key factors for organ allocation is based on the severity of chronic liver disease. For a pediatric liver transplant candidate, the severity of illness is characterized by the pediatric end-stage liver disease (PELD) score that predicts the 3-month probability of wait-list death (i.e., death without receiving a transplant) (McDiarmid et al., 2004). The PELD score has been used by the UNOS for prioritizing liver allocation since February 2002. Patients with higher PELD scores correspond to poorer prognosis, hence they will have higher priority to receive donated organs. The PELD score was originally developed from a Cox proportional hazards model and the transplant recipients were treated as noninformative censoring, which implicitly assuming that transplant and wait-list death are independent events. However, this assumption of independence seems dubious because that patients with worse prognosis tend to be prioritized to receive transplants. It is more appropriate to consider a positive correlation structure between the transplant and the underlying death process. Another issue with the current PELD scoring system is that only measurements at baseline are incorporated into the original prediction model. In the liver transplant community, researchers are more concerned about the association between fluctuations in prognostic factors over time and the underlying mortality process. Therefore, a model in which time average effects or time-varying effects can be examined should be constructed. In this study, we applied our proposed method to estimate the 90-day mortality in patients who were awaiting transplant in order to address the issues of positive dependence between the main event and the competing event as well as incorporating time-dependent information in predictions.

We used a dataset consisting of 3,221 pediatric patients who were on the UNOS transplant waiting list from February 27, 2002 through June, 2010. The data were extracted from the original UNOS dataset by excluding patients who were initially listed with a model for end-stage liver disease (MELD) risk score, or were 12 year old or older, or were inactive (i.e., Status 7), or were at risk of imminent death (i.e., Status 1), or had acute liver disease, or had a primary diagnosis of cancer, or those who eventually received a multiorgan transplant. Most patients in the final analytic sample were infants under 1 year old (58%), female (51%), and white (50%). The median follow-up time was 76 days. At the end of the follow-up, 332 (10%) patients died before receiving a transplant; 2,207 (69%) patients received transplantations; and the remaining 682 (21%) patients were censored because that they were either removed from the waiting list for other reason or were still waiting for transplantation before the end of follow-up.

To check the RSC assumption of this dataset, we examined the normalized subsurvival distributions of death and transplant ($\tilde{S}_1(t)$ and $\tilde{S}_2(t)$, respectively) estimated using the IPCW Kaplan-Meier estimator (2.1). As a result, the subsurvival of the wait-list mortality does not dominate that of the transplant, which indicates a violation of the RSC. Because there was a high percentage of infants (< 1 year old) in the dataset, we analyzed infants and noninfant kids separately and the two subsurvival distributions overlay after being stratified by age (< 1 and ≥ 1) (shown in Figure 4.1). When this heuristic graphical method was used to test the null hypothesis of the RSC assumption, we did not have enough evidence to reject the null hypothesis and concluded that the distribution of transplant does not dominate that of death. Therefore, we investigated risk factors and estimated the marginal survival functions separately for patients aged < 1 year old vs. patients aged ≥ 1 year old. Note that the above-mentioned graphical verification of RSC is a heuristic method and the formal analytic tests will to be derived later.

Among patients in the < 1 age group, 51% were female, 48% white. The median follow-up time was 72 days. At the end of follow-up, 247 (13%) patients died before receiving a transplant; 1,282 (68%) patients received transplantation; and the remaining 346 (19%) patients were censored. Among patients in the ≥ 1 age group, 51% were female, 57%white. The median follow-up time was 84 days. At the end of follow-up, 85 (6.0%) patients died before receiving a transplant; 925 (69.0%) patients received transplantation; and the remaining 336 (25.0%) patients were censored.

For comparison, we fit another two models for each of the two above-mentioned age groups. The first model was the RSC model proposed by Yabes (2012). No observations were truncated because of the extreme values of weight. The second model was the Cox proportional hazards model treating transplant as independent censoring. By fitting the latter model, we implicitly assumed that death and transplant were independent events. For both models we examined the potential risk factors including etiology of liver disease (autoimmune disorder, metabolic disorder, biliary atresia [BA], and others), presence/absence of encephalopathy, growth failure, and laboratory measurements (log-transformed total bilirubin level, log-transformed albumin level, and log-transformed international normalized ratio [INR]).

Tables 4.1 and 4.2 summarize the results from these two models stratified by age (Table 4.1 for age $<$ 1 year and Table 4.2 for age $\geq$ 1 year). For both age groups, the risk factors identified by the RSC regression model (RSC) and by our proposed model (RSC-Psuedo) were similar but were different from those identified by the Cox proportional hazards regression model (COX). In those analyses which transplantation was treated as independent censoring (COX), we found that the presence of growth failure, presence of encephalopathy, a higher total bilirubin level, a lower albumin level, and a higher INR corresponded to a significant increase in the risk of wait-list mortality. These covariates constitute the PELD score. When we fit the regression model using our proposed method (RSC-Pseudo), we found that the mortality risk increased with a higher INR, presence of encephalopathy, or a higher total bilirubin level. For the age $<$ 1 group, although albumin level was significantly associated with wait-list mortality in the RSC model and was at borderline significance (p-value $<$ 0.1) in the RSC-Pseudo model, the effect sizes of albumin in these two models were very close.

Goodness of fit of the RSC-Pseudo models were evaluated by comparing the IPCW Kaplan-Meier subsurvival function in (2.3) with marginal survival estimates in (2.10). As show in Figure 4.2, the survival curves between the two indicate a lack of fit. This means that bilirubin, albumin, INR, disease type, encephalopathy, growth failure, and age can explain only a part of the variation of pretransplant survival. Additional covariates may be needed to improve the fit. We also presented those survival functions derived from the Cox proportional hazards models for comparison. The large deviations between the Cox survival curves and the IPCW Kaplan-Meier curves indicate a lack of fit of the Cox models.

To incorporate time-varying covariates and estimate their effects on marginal survival, we first selected time points of interest then calculated pseudo-values for each individual in the entire sample for these time points. A generalized linear model was then fitted to obtain the estimated covariate effects. Two types of covariate effects were examined: the average time effects and time-varying effects. Assume that J time points were selected to calculate pseudo-values. For the model estimating average time effects, we had $(p + J)$ (p is the number of time-varying covariates) unknown regression parameters to be estimated. For the model estimating time-varying effects, we had $(p+1)\times J$ unknown regression parameters to be estimated.

We examined the average time effects of three variables: bilirubin, INR, and albumin, at 12 selected time points. In addition, we fit piecewise-constant models to examine the variation in covariate effects over four time intervals: from baseline to 90 days, 91 days to 180 days, 181 days to 270 days, and 271 days to 360 days in two age groups. When we fit the model using the c-log-log link for the age ≥ 1 group, the model had an issue in convergence because of small sample size. We then changed the link to identity and refit the models for the two age groups. Figure 4.3 depicts the time-varying effects of the covariates on marginal survival function, using identity link functions for the two age groups. The solid black line represents piecewise-constant effects over time and the dashed red line represents the average effects over time. In the age < 1 group, the effects of albumin and bilirubin fluctuates around their average effects, while the effects of INR increases over time. In the age ≥ 1 group, effects of all three variables fluctuates around their average effects.

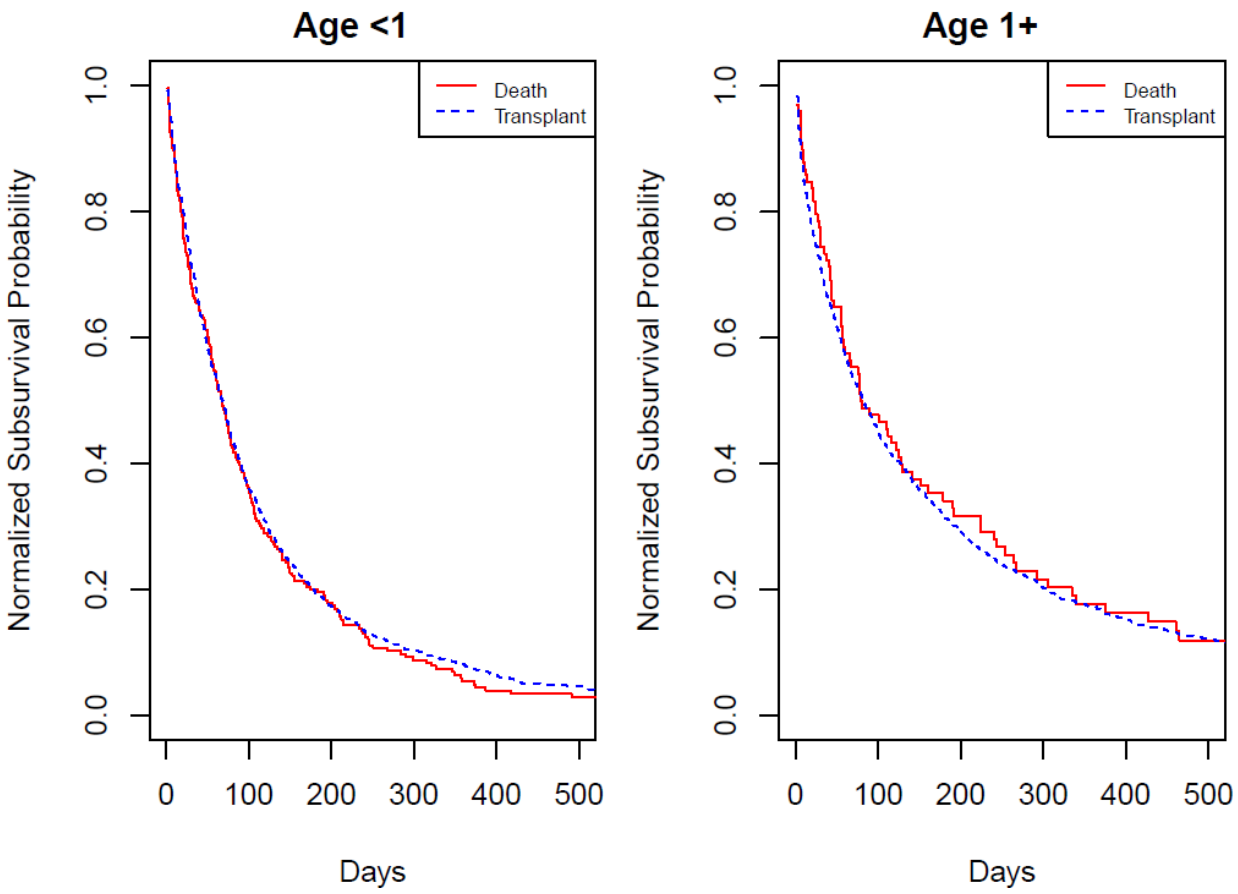

Figure 4.1: Verification of the Random Signs Censoring Assumption in the Liver Transplant Data Stratified by Age Group

Table 4.1: Analysis Results for the Liver Transplant Data (Age under 1)

Variable (Reference)	Level	RSC-Pseudo		RSC		Cox	
		Coef±SE	HR(p-value)	Coef±SE	HR(p-value)	Coef±SE	HR(p-value)
Log Bilirubin		0.15 ± 0.08	1.17 (0.05)	0.47 ± 0.10	1.59 (<.001)	1.01 ± 0.11	2.74 (<.001)
Log Albumin		-0.66 ± 0.38	0.52 (0.088)	-0.84 ± 0.27	0.43 (0.006)	-1.94 ± 0.28	0.14 (<.001)
Log INR		2.51 ± 0.36	12.30 (<.001)	1.50 ± 0.17	4.47 (<.001)	0.69 ± 0.13	1.99 (<.001)
Growth Failure (No)	Yes	-0.24 ± 0.19	0.79 (0.213)	-0.22 ± 0.12	0.80 (0.172)	0.67 ± 0.13	1.95 (<.001)
Disease Group	Autoimmune	-0.42 ± 0.68	0.66 (0.541)	0.26 ± 0.34	1.29 (0.540)	0.70 ± 0.36	1.91 (0.056)
(BA)	Metabolic	-0.53 ± 0.36	0.59 (0.136)	-0.02 ± 0.30	0.98 (0.956)	0.67 ± 0.31	1.95 (0.033)
	Other	-0.34 ± 0.28	0.71 (0.226)	-0.10 ± 0.15	0.90 (0.610)	0.25 ± 0.16	1.28 (0.131)
Encephalophaty (No)	Yes	1.45 ± 0.50	4.27 (0.004)	1.41 ± 0.35	4.08 (<.001)	1.13 ± 0.35	3.11 (0.001)

RSC-Pseudo for proposed model; RSC for inverse probability censoring weights model; COX for competing event as independent censoring.

Table 4.2: Analysis Results for the Liver Transplant Data (Age 1 or older)

Variable (Reference)	Level	RSC-Pseudo		RSC		Cox	
		Coef±SE	HR(p-value)	Coef±SE	HR(p-value)	Coef±SE	HR(p-value)
Log Bilirubin		0.34 ± 0.14	1.41 (0.015)	0.42 ± 0.12	1.52 (0.003)	0.85 ± 0.13	2.34 (<.001)
Log Albumin		0.54 ± 0.81	1.72 (0.505)	0.34 ± 0.35	1.40 (0.463)	-1.19 ± 0.38	0.30 (0.002)
Log INR		1.37 ± 0.41	3.92 (<.001)	1.71 ± 0.41	5.53 (<.001)	0.58 ± 0.29	1.78 (0.050)
Growth Failure (No)	Yes	-0.64 ± 0.36	0.53 (0.083)	-0.30 ± 0.23	0.74 (0.468)	0.72 ± 0.25	2.06 (0.003)
Disease Group	Autoimmune	0.02 ± 0.61	1.02 (0.978)	0.36 ± 0.36	1.43 (0.469)	-0.07 ± 0.41	0.93 (0.862)
(BA)	Metabolic	0.60 ± 0.31	1.83 (0.049)	1.55 ± 0.60	4.71 (0.036)	-0.47 ± 0.61	0.63 (0.445)
	Other	-0.09 ± 0.32	0.77 (0.912)	0.44 ± 0.23	1.55 (0.082)	0.25 ± 0.27	1.28 (0.362)
Encephalophaty (No)	Yes	3.29 ± 0.81	26.9 (<.001)	1.95 ± 0.58	7.00 (<.001)	0.85 ± 0.38	2.33 (0.024)

RSC-Pseudo for proposed model; RSC for inverse probability censoring weights model; COX for competing event as independent censoring.

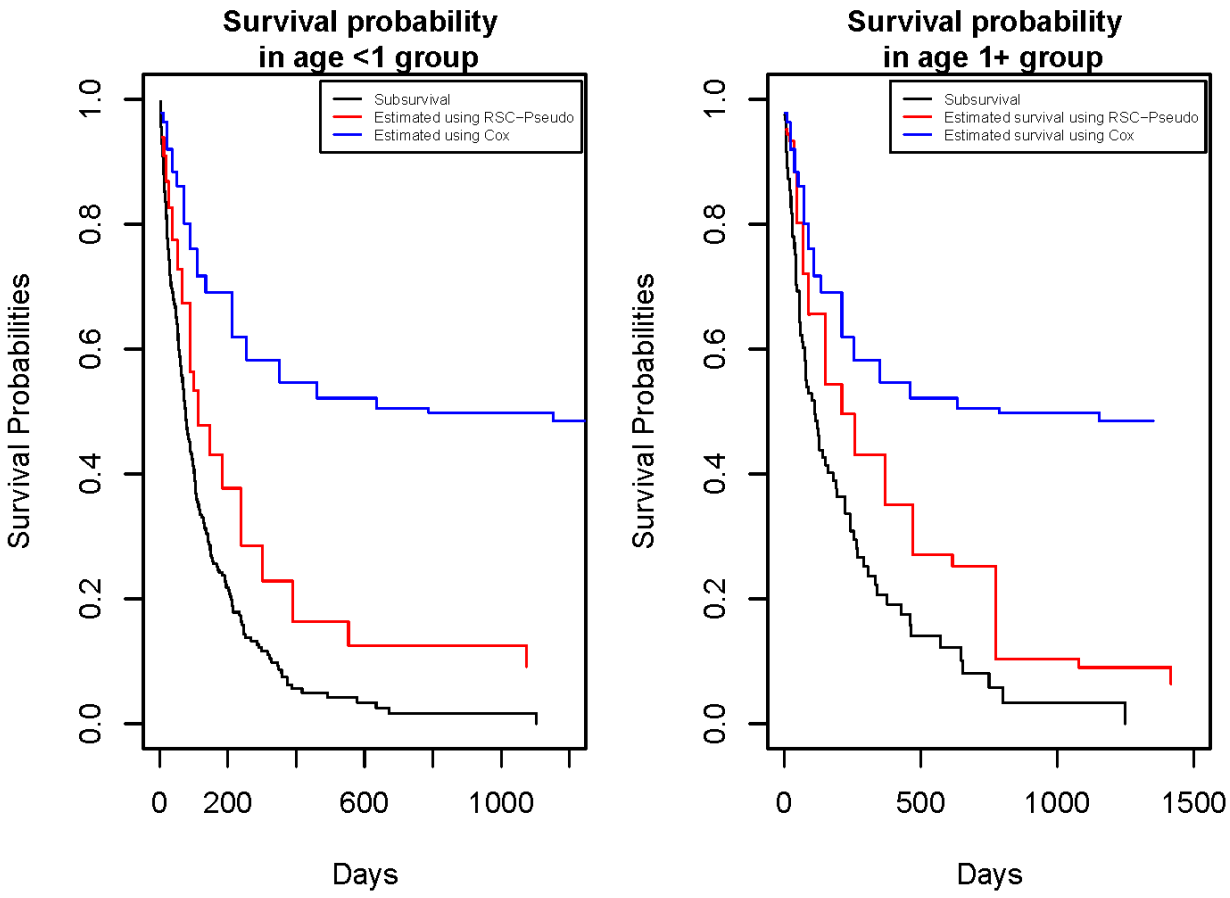

Figure 4.2: Goodness of Fit of the Models

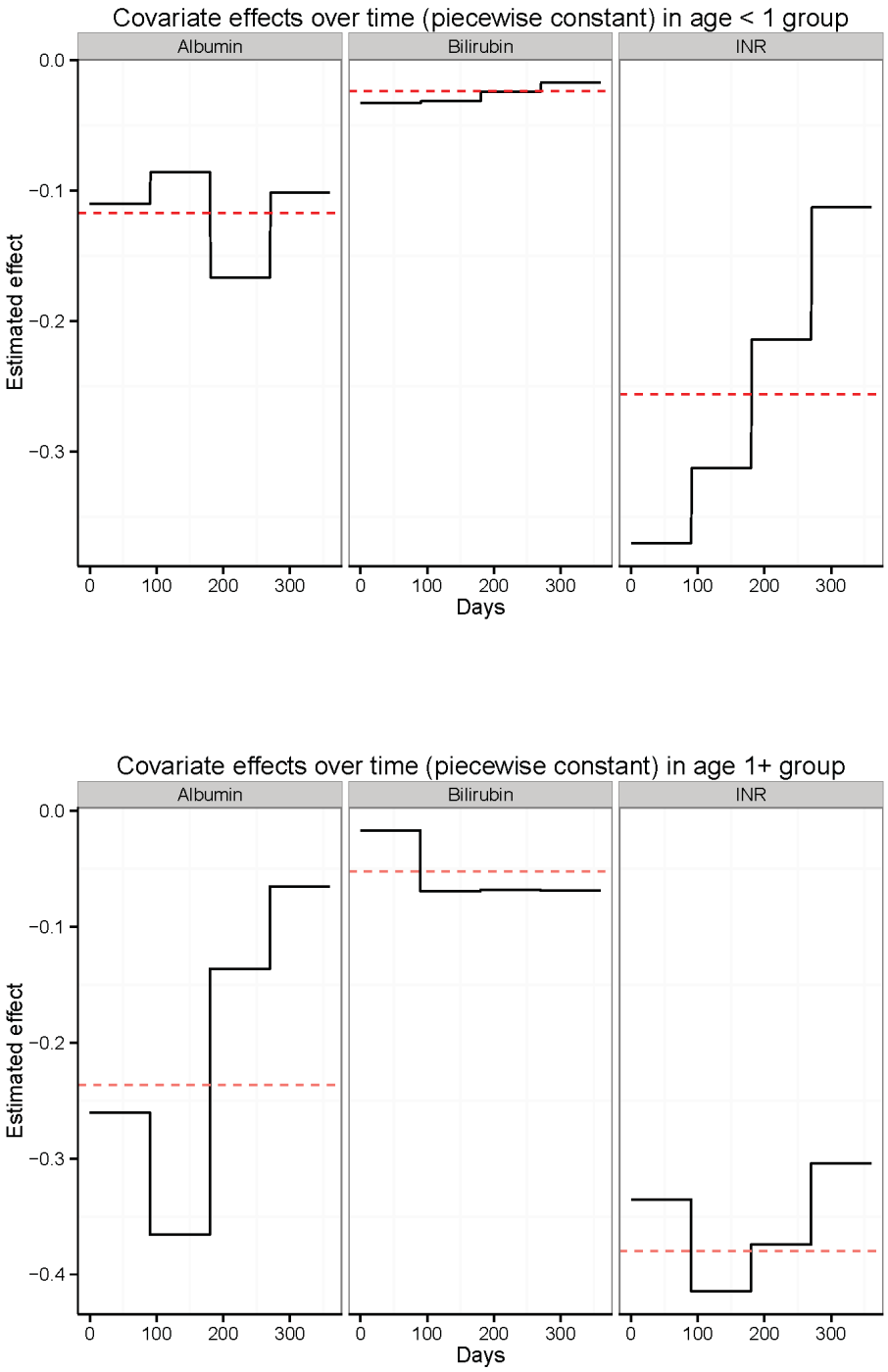

Figure 4.3: Estimated Effect over Time in Two Age Groups using Identity Link. The solid black line represents piecewise constant effect over time and dashed red line represents the average effect over time.

5.0 DISCUSSION

In this study, we proposed a method that can be used to estimate marginal survival function and the corresponding covariate effects for data with competing risks. The method uses the pseudo-values approach to handle the missing information due to independent censoring and it is under the assumption of random signs censoring for competing risks. Unlike most of the currently available methods in which assumptions are imposed on the structure of the relationship among failure times of the competing events, in our method the random signs censoring assumption is verifiable from the observed data.

Although there are many survival regression models existing, a generalized linear model approach is always appealing because of its well-known properties and easy implementation. Andersen et al. (2003) proposed a pseudo-value method to create a pseudo dataset which is a dataset with complete information from the original incomplete data resulted from non-informative censoring. Later, Klein and Andersen (2005) applied a standard generalized linear model on the pseudo dataset to estimate the cumulative incidence function (crude probability in the presence of other competing events). An advantage of this approach is that graphic displays may be constructed easily when assessing goodness of fit of the models (e.g., proportional hazard models) Perme and Andersen (2008). Given that pseudo-values are defined at multiple selected time points for every subjects, estimated covariate effects of potential factors can be obtained by solving the corresponding generalized estimating equation. Various choices of link function and distributions of the failure time can be considered for the corresponding generalized linear model. In order to obtain a stable estimator, Klein and Andersen, 2005 suggested choosing 5 to 10 grid time points.

Under the assumption of random signs censoring, we applied the pseudo-values approach to handle noninformative censoring and estimated covariate effects and the marginal survival

function by using a generalized linear model. We have shown that the estimated covariate effects for the proposed model are consistent and asymptotically normally distributed. We proved that the pseudo-values derived from the IPCW Kaplan-Meier estimator met conditional unbiasedness. Results of the simulation studies indicated that under the assumed model, the proposed procedure performs well with small bias and have a reasonable coverage probability. Although the bias of the proposed estimators are slightly larger than the original RSC model, the coverage probabilities maintain well even under high proportions of censoring or competing events. The performance of the Cox model becomes worse as the proportions of the competing events increase, which is predictable since treating competing events as noninformative censoring will deviate more when the proportions of competing risks increase. We also showed that marginal survival can be estimated using equation (2.11) and derived the standard errors of this estimator using the delta method. One can then make inference on the estimated marginal survival function. Simulations were conducted to evaluate the performance of this estimator. The results show that the bias is relatively low and acceptable.

We used the proposed model to estimate average covariate effects and time-varying covariate effects. The implementation is easy and straightforward using standard statistical package. However, we found that when fitting models on small datasets such as the ≥ 1 age group in the liver transplant data, estimating time-varying covariate effects could be a problem using the c-log-log link function. One possible explanation is that the proportional hazard assumption inherited in c-log-log link is not appropriate for this dataset. We found that models using the identity link can provide stable estimates. If a link function other than the c-log-log one is used, the regression coefficients of the model do not have direct interpretations like the log baseline cumulative hazards or log hazard ratios using c-log-log link.

Andersen et al. (2004) pointed out that the selection of grid time points for longitudinal analyses, characteristics of the data, such as the number of failures and the pattern of the event times, should be taken into consideration for models built upon pseudo-values. Although the proposed method works well in general, one limitation of the proposed method is that it may not be computationally efficient if a large number of time points are used to

calculate pseudo-values. Also, if we have K time points of interest, we will need to fit K generalized linear models. To bypass this, we may incorporate a smooth function to estimate the pattern of covariate effects in one step. Further investigations of model characteristics are needed on the use of different link functions and the potential influences of sample size and power. Asymptotic properties of the estimated variance of marginal survival functions also need to be evaluated using simulation studies.

For future work on liver transplant data analyses, we need to reevaluate and identify important risk factors on marginal survival from all available variables in the data. The estimated marginal survival function based on significant risk factors can then be used as the risk estimate for each transplant candidate. We will also evaluate the concordance between the risk based on the observed survival (derived from the IPCW Kaplan-Meier method) and the ranking based on the adjusted marginal survival (derived from the proposed model). If there exists a high degree of agreement between the two survival estimates are, the risk estimates derived from our models can be used to prioritize the patients on the transplant waiting list.

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