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A proportional hazards regression model for the subdistribution with covariates adjusted censoring weight for competing risks data

PENG HE
Division of Biostatistics, Medical College of Wisconsin, U.S.A.

THOMAS H. SCHEIKE
Department of Biostatistics, University of Copenhagen, Denmark

MEI-JIE ZHANG
Division of Biostatistics, Medical College of Wisconsin, U.S.A.

ABSTRACT. With competing risks data, one often needs to assess the treatment and covariate e ects on the cumulative incidence function. Fine and Gray proposed a proportional hazards regression model for the subdistribution of a competing risk with the assumption that the censoring distribution and the covariates are independent. Covariate-dependent censoring sometimes occurs in medical studies. In this paper, we study the proportional hazards regression model for the subdistribution of a competing risk with proper adjustments for covariate-dependent censoring. We consider using a covariate-adjusted weight function by tting the Cox model for the censoring distribution and using the predictive probability for each individual. Our simulation study shows that the covariate-adjusted weight estimator is basically unbiased when the censoring time depends on the covariates, and the covariate-adjusted weight approach works well for the variance estimator as well. We illustrate our methods with bone marrow transplant data from the Center for International Blood and Marrow Transplant Research (CIBMTR). Here cancer relapse and death in complete remission are two competing risks.

key words: competing risks; cumulative incidence function; proportional hazards model; subdistribution; inverse probability of censoring weight

1 Introduction

$P(C > t)$, where C is the censoring time. Fine and Gray's approach is based on the fact that $E[r(t)=G_C f(\tilde{T} \wedge C) \wedge t | Data] = 1$ provided that censoring time is independent of the covariates, and FG proposed using the Kaplan-Meier estimator to estimate the unknown censoring distribution G_C. However, in biomedical research studies, the censoring time may depend on some of the covariates and the treatment group. In a clinical trial, patients may be more likely to drop out with some specific value of covariate characteristics, and one treatment group may have a higher dropout rate than the others (Mai, 2008). DiRienzo & Lagakos (2001a,b) showed when the distribution of censoring depends on both treatment group and the covariates, in general the null asymptotic distribution of the score test is not centered at zero when the model is misspecified, the tests of treatment group effect can be severely biased. Heinze et al. (2003) showed that if the censoring distributions are not similar in the two comparison groups, the log-rank test and fitting a regression model, such as fitting a proportional hazards model, may not be valid. For the competing risks data, one can show that $E[r(t)=G_C f(\tilde{T} \wedge C) \wedge t | Data | Data] = 1$, where $G_C f(\tilde{T} \wedge C) \wedge t | Data$ is the conditional censoring distribution given by Data. Thus, parameter estimates using the inverse probability of censoring weighting approach with the Kaplan-Meier estimator may be biased when the censoring distribution depends on some of the covariates. To adjust the IPCW when censoring distribution depends on some of the covariates, Fine & Gray (1999) suggested using a stratified Kaplan-Meier estimator for the discrete covariates and assuming the Cox model for the continuous covariates. In this study, we considered a regression model for the censoring distribution, such as a Cox proportional hazards model,

competing risks data structure. We introduce a regression-adjusted inverse weighted estimation for the proportional subdistribution hazards model and present the asymptotic results that can be used for inference. Simulation studies are provided in Section 3. In Section 4 we analyze two real data sets, which were originally studied by Kumar et al. (2012) and by Ringden et al. (2012) using data from the Center for International Blood and Marrow Transplant Research (CIBMTR). Concluding remarks are provided in Section 5.

2 Data and covariate adjusted censoring weight

Let $\tilde{T}_i$ and C_i be the event time and right censoring time for ith individual, respectively. $_i \ 2 \ f1;::::;Kg$ indicates the cause of failure. For simplicity, we assume $K = 2$ in this study. Let $T_i = \min(\tilde{T}_i; C_i)$ and $_i = I(\tilde{T}_i \quad C_i)$. We observe n independent and identically distributed (i:i:d:) data $f T_i; \ _i; \ _i \ _i; Z_i g$ for $i = 1;::::;n$, where $Z_i = (Z_{i1};::::;Z_{iq})^T$ are associated covariates. We assume that $(\tilde{T}_i; \ _i)$ are independent of C_i given covariates of Z_i. We are interested in modeling the cumulative incidence function of cause 1, $F_1(t; Z)$. Based on Gray (1988b) subdistribution hazard technique, Fine & Gray (1999) proposed a proportional subdistribution hazards model

$$_1(t; Z) = \frac{d \log f 1 \quad F_1(t; Z)g}{dt} = \ _{10}(t) \exp \quad {}^T_0 Z \quad : \tag{2.1}$$

There is a direct relationship between the CIF and subdistribution hazard function:

$$F_1(t; Z) = 1 \quad \exp \quad \int_0^{Z_t} \ _{10}(u)du \quad e^{\ {}^T_0 Z} \quad :$$

Let $N_i^1(t) = I(\tilde{T}_i \quad t; \ _i = 1)$ be the underlying counting process associated with cause 1. For right censored competing risks data, $N_i^1(t)$ and $Y_i^1(t) = 1 \quad N_i^1(t \ )$ are not fully observed. For a censored individual, it is only observed up to the censoring time C_i. De ne $r_i(t) = I f C_i \quad (\tilde{T}_i \wedge t)g$. Then, $r_i(t)N_i^1(t)$ and $r_i(t)Y_i^1(t)$ are computable for all time t. Let

$G_C(t;Z) = P(C \quad tjZ)$ be the conditional censoring distribution. Based on

$$
\begin{aligned}
E \quad \frac{r_i(t)N_i^1(t)}{G_C(T_i \wedge t;Z_i)} &= E \quad E \quad \frac{r_i(t)N_i^1(t)}{G_C(T_i \wedge t;Z_i)} \quad Z_i \\
&= E \quad N_i^1(t)jZ_i \quad \frac{E\{r_i(t)jZ_i\}}{G_C(T_i \wedge t;Z_i)} \\
&= F_1(t;Z_i)
\end{aligned}
$$

FG proposed using an inverse probability of the censoring weighting (IPCW) approach to t the model (2.1) and proposed an IPCW weight function $w_i^{KM}(t) = r_i(t)\hat{G}_C^{KM}(t) = \hat{G}_C^{KM}(T_i \wedge t)$, where $\hat{G}_C^{KM}(t)$ is the Kaplan-Meier estimator for the unknown censoring distribution. FG proposed estimating the unknown regression coe cient by solving the score equation

$$U_{KM}(\quad) = \sum_i \int_0^{Z_i} \left(\quad \sum_j w_j^{KM} (u \quad 11.9552 \; Tf \; 14.09 \; 2. \; Z \right.$$

$G_C(t;X) = P(C > t|X)$ by

$$\hat{G}_C^{COX}(t;X) = \exp\left\{-\hat{\Lambda}_{C0}(t)\exp\left(\hat{\beta}^T X\right)\right\}; \qquad (2.2)$$

where $\hat{\beta}$ is a maximum partial likelihood estimate for β_0 and $\hat{\Lambda}_{C0}(t)$ is a standard Nelson-Aalen type estimator for the cumulative baseline censoring hazard $\Lambda_{C0}(t) = \int_0^t \lambda_{C0}(u)du$. In this study, we considered a covariates-adjusted IPCW weight function

$$w_i^{COX}(t) = r_i(t)\hat{G}_C^{COX}(t;X_i) = \hat{G}_C^{COX}(T_i \wedge t;X_i).$$

We estimated β in model (2.1) by solving the score equation

$$U_{COX}(\beta) = \sum_i \int_0^\infty Z_i - \frac{\sum_j w_j^{COX}(u)Y_j^1(u)Z_j\exp\{\beta^T Z_j\}}{\sum_j w_j^{COX}(u)Y_j^1(u)\exp\{\beta^T Z_j\}} w_i^{COX}(u)dN_i^1(u) = 0;$$

and denoted the estimate as $\hat{\beta}_{COX}$. Then we estimated $\Lambda_{10}(t)$ by

$$\hat{\Lambda}_{10}^{COX}(t) = \sum_i \int_0^t \frac{w_i^{COX}(u)dN_i^1(u)}{\sum_j w_j^{COX}(u)Y_j^1(u)\exp\left\{\hat{\beta}_{COX}^T Z_j\right\}}.$$

Under regularity conditions, it can be shown that $\sqrt{n}\left(\hat{\beta}_{COX} - \beta_0\right)$ converges in distribution to a mean zero Gaussian distribution with an asymptotic variance that can be estimated by

$$\hat{\beta}^{COX} = n\sum_i$$

$\hat{F}_1^{KM}(t;Z) = 1 - \exp\left\{-\hat{\Lambda}_{10}^{KM}(t)\exp\left(\hat{\beta}_{KM}^T Z\right)\right\}$ or $\hat{F}_1^{COX}(t;Z) = 1 - \exp\left\{-\hat{\Lambda}_{10}^{COX}(t)\exp\left(\hat{\beta}_{COX}^T Z\right)\right\}$, respectively. Fine & Gray (1999) derived the large sample property for $\sqrt{n}\left\{\hat{F}_1^{KM}(t;Z) - F_1(t;Z)\right\}$ when the censoring distribution is independent of the covariates. When the censoring distribution depends on the covaraites through a Cox model, by functional Delta method, we can show that $\sqrt{n}\left\{\hat{F}_1^{COX}(t;Z) - F_1(t;Z)\right\}$ converges in distribution to a Gaussian process with asymptotic variances, which can be estimated by

$$n\sum_i^n \left\{\hat{F}_1^{COX}(t;Z)\right\}^2 \left\{\hat{W}_{F_1;i}^{COX}(t;Z)\right\}^2;$$

where

$$\hat{W}_{F_1;i}^{COX}(t;Z) = \exp\left(\hat{\beta}_{COX}^T Z\right)\left\{\hat{\Lambda}_{10}^{COX}(t)\,\hat{W}_{;i}^{COX\ T} Z + \hat{W}_{;i}^{COX}(t)\right\}:$$

Resampling techniques can be used to construct con dence bands for $_{10}(t)$ and $F_1(t;Z)$ (Lin et al., 1994; Scheike et al., 2008).

3 Simulations

We compared the nite-sample performance of the estimator using the covariate-adjusted censoring weight to the unadjusted estimator using the Kaplan-Meier estimator for the censoring distribution. Two simulation studies were considered to examine the potential bias reduction with the covariate-adjusted censoring weight estimator. For the rst study, we had one binary covariate. For the second study, we considered one binary covariate and one continuous covariate. In both studies, we compared the performances of estimators using two weights, $w_i^{KM}(t)$ and $w_i^{COX}(t)$, respectively.

3.1 Study 1

The regression model below has one binary covariate Z. Given Z, the cumulative incidence functions are given by

$$F_1(t;Z) = 1 \quad 1 \quad p \quad 1 \quad e^{\ t} \quad \text{exp9552 Tf 4.5syh7}$$

where $p = F_1(1j\ Z = 0)$. We let $p = 0{:}66$ and Z be a Bernoulli random variable, with a value 1 for half of the sample and 0 for the other half. We set $\quad = 1$ and considered the following three simulation scenarios.

Scenario 1	Censoring times are independent of Z: Generate censoring times from an exponential distribution $\quad \exp(\ _C)$ Set $\ _C = 0{:}556$ for 30% censoring, $\ _C = 1{:}342$ for 50% censoring
Scenario 2	Censoring times depend on Z by a Cox model: Generate censoring times from a Cox model, $\ _C(tjZ) = \ _C \exp(\ _C Z)$ Set $\ _C = 2{:}5$ and $\ _C = 0{:}137$ for 30% censoring Set $\ _C = 2{:}5$ and $\ _C = 0{:}391$ for 50% censoring
Scenario 3	Censoring times depend on Z, not by a Cox model: $C \ s\ U(0{:}25; 4{:}00)$, if Z

satisfactory results in estimating the covariate e ect and cumulative baseline subdistribution hazard function. Both estimators also have almost identical sample standard deviation and similar MSE, which indicate that the potential e ciency losses are minimum when using covariate-adjusted censoring weight.

3.2 Study 2

The regression models below have one binary covariate Z_1 and one continuous covariate Z_2. Given Z_1 and Z_2, the cumulative incidence functions are given by

$$F_1(t; Z_1; Z_2) = 1 \quad 1 \quad p \; 1 \quad e^{\,t \quad \exp(\ _1 Z_1 + \ _2 Z_2)}$$

and

$$F_2(t; Z_1; Z_2) = (1 \quad p)^{\exp(\ _1 Z_1 + \ _2 Z_2)} \; 1 \quad e^{\,t \exp(\ _1 Z_1 + \ _2 Z_2)} :$$

We let $p = 0{:}66$, and Z_1 is a Bernoulli random variable, with a value 1 for half of the sample and 0 for the other half. Z_2 is a $N(0; 1)$ random variable. We set $_1 = 1$; $_2 = 0{:}5$ and considered the following four scenarios.

Scenario 1	Censoring times are independent of Z_1 and Z_2 Generate censoring times from an exponential distribution exp($_C$) Set $_C = 0{:}547$ for 30% censoring, $_C = 1{:}352$ for 50% censoring
Scenario 2	Censoring times depend on Z_1 by a Cox model Generate censoring times from $_C(t\|Z) = \ _C \exp(\ _{C1} Z_1)$ Set $_{C1} = 2{:}5$. Set $_C = 0{:}137$ for 30% censoring, $_C = 0{:}397$ for 50% censoring
Scenario 3	Censoring times depend on Z_1 and Z_2 by a Cox model Generate censoring times from $_C(t\|Z) = \ _C \exp(\ _{C1} Z_1 + \ _{C2} Z_2)$ Set $_{C1} = 2{:}5$, $_{C2} = 2{:}5$. Set $_C = 0{:}082$ for 30% censoring, $_C = 0{:}389$ for 50% censoring
Scenario 4	Censoring times depend on Z_1, not by a Cox model C s $U(0{:}25; 4{:}00)$, if $Z_1 = 0$, C s $U(0{:}07; 1{:}14)$, if $Z_1 = 1$ for 30% censoring C s $U(0{:}25; 2{:}00)$, if $Z_1 = 0$, C s $U(0{:}06; 0{:}438)$, if $Z_1 = 1$ for 50% censoring

For each setting, we simulated 10,000 replicates with n = 100 and 300. The regression coe cients $_1$ and $_2$

versus 0 for HLA-identical sibling (N=584)), and prior autologous transplant (PREAUTO: 1 for Auto+Allo transplant (N=399) versus 0 for allogeneic transplant alone (N=465)).

First, we fit a Cox model for the censoring distribution where relapsed or dead individuals are considered as censoring subjects. The hazard ratios (HR) are: HR(GRP)=6.42 ($P < 0.0001$); HR(DNR)=0.48 ($p = 0.0018$); HR(PREAUTO)=1.73 ($p = 0.0013$). These results indicate that the censoring distribution depends on the transplant time period, donor type and prior autologous transplantation. Next, we fit a proportional subdistribution hazards model (2.1) with the Kaplan-Meier estimated unadjusted weight and the Cox model adjusted weight, and we computed the predicted cumulative incidence probability for a patient who received an HLA-identical sibling donor allogeneic transplantation in 1995-2000 or in 2001-2005 (see results in Table 3-4 and Figure 3). Both weights give similar estimates for TRM. However, for cancer relapse, the regression estimate of the main treatment effect are $\hat{\alpha} = 0.38$ and $\hat{\alpha} = 0.54$ by unadjusted weight and Cox model adjusted weight, respectively. At three years after transplant, the differences in cumulative incidence of relapse between late and early transplant (TX) patients are 0.09 (CIF=0.34 for the late TX versus CIF=0.25 for the early TX) and 0.13 (CIF=0.35 for the late TX versus CIF=0.22 for the early TX) by unadjusted weight and Cox model adjusted weight, respectively. The unadjusted weight underestimates the effect size of CIF of relapse by 4% compared to the point estimate using the Cox model adjusted weight (Table 4). Underestimated effect size counts about 14% (0.04/((0.22+0.35)/2)) of estimated average CIF, which leads to quite a large relative bias.

4.2 Example 2

We considered another CIBMTR study data set (Ringdén et al., 2012) that consists of 177 myeloma patients who received a reduced-intensity conditioning allogeneic transplantation. Cancer relapse and TRM were two competing risks in this study. 105 patients received prior autologous transplant, and 72 patients received allogeneic transplant alone. We were interested in transplant type effect on relapse and TRM. Let PREAUTO be the indicator of transplant type (1 for Auto+Allo transplant versus 0 for Allogeneic transplant alone). Here the

reduces a relative bias of 17% ((0:41 0:34)=0:41).

5 Concluding remarks

We have shown that the estimator using the Kaplen-Meier estimated unadjusted inverse probability of censoring weight is not asymptotically unbiased when the censoring distribution depends on the covariates and the biases could be signi cant for xed sample sizes. We considered a regression model for the censoring distribution, and we considered using the Cox proportional hazards model and predicted censoring weight for each individual. We have illustrated that the Cox model adjusted weight works well when censoring distribution depends on the covariates, and potential e ciency losses are minimal for both independent and dependent censoring cases. With the transplant data, we determined that the covariate-adjusted weight can be adopted to reduce bias. We are working on an R package, which will be available to the public.

In this study, we only considered using the most common Cox proportional hazards model for the censoring distribution. The Cox model requires a proportional e ect (constant e ect) for each covariate. However, the proportionality assumption may not be true for some of the covariates. When the Cox model does not t the data well, one may consider alternative regression models for the censoring distribution. An alternative model-based weight function needs be considered, an e cient variance estimator needs to be derived, potential bias reduction needs to be studied, and a computing package needs to be further developed as well.

Recently, the inverse probability of censoring weighting (IPCW) technique (Robins & Rotnitzky, 1992) has been used extensively for right-censored survival data and, speci cally, for completing risks data. It has been shown that regression modeling of the censoring distribution can be used to improve the e ciency of the IPCW technique (Bickel et al., 1993; Van der Laan & Robins, 2003; Scheike et al., 2008) even if the censoring distribution is independent of the covariates. In this study, we showed that the covariate-adjusted IPCW technique can be used to reduce bias for modeling the subdistribution hazard function when censoring depends on the covariates. In general, the covariate-adjusted IPCW technique should be considered to improve e ciency and reduce bias.

6 Appendix

Here we give a brief derivation for the variance estimation for $\sqrt{n}\,(\hat{\beta}_{COX} - \beta_0)$ and $\sqrt{n}\,(\hat{\beta}^{COX}_{10}(t) - \beta_{10}(t))$, and give explicit expressions for b_i^{COX}; b_i^{COX} and $W_{;i}^{COX}(t)$. Let $M_i^1(t) = N_i^1(t) - \int_0^t Y_i^1(u)\exp(\beta_0^T Z_i)\, d\beta_{10}(u)du$, which is a zero mean martingale for complete data. Assuming the censoring distribution depends on covariates X through a Cox proportional hazards model where X could be a subset covariates of Z,

$$\lambda_C(t; X) = \lambda_{C0}(t)\exp(\beta_0^T X).$$

By Taylor's approximation,

$$\sqrt{n}\,(\hat{\beta}_{COX} - \beta_0) = \sqrt{n}\, I_{COX}(\hat{\beta}_{COX})^{-1} U_{COX}(\beta_0) + o_p(1); \tag{6.1}$$

where

$$U_{COX}(\beta_0) = \sum_i \int_0^\infty (Z_i - E_{COX}(\beta_0; u)) w_i^{COX}(u) dM_i^1(u)$$

$$= \sum_i \int_0^\infty (Z_i - E_{COX}(\beta_0; u)) r_i(u) \frac{G_C(u; X_i)}{G_C(T_i \wedge u; X_i)} dM_i^1(u) \tag{6.2}$$

$$+ \sum_i \int_0^\infty \left(\frac{\theta_C^{COX}(u; X_i)}{\theta_C^{COX}(T_i \wedge u; X_i)} - \frac{G_C(u; X_i)}{G_C(T_i \wedge u; X_i)} \right) (Z_i - E_{COX}(\beta_0; u)) r_i(u) dM_i^1(u) \tag{6.3}$$

$$I_{COX}(\beta) = \partial U_{COX}(\beta)/\partial \beta \tag{6.4}$$

and

$$S^{(k)}_{COX}(\beta; u) = \sum_i w_i^{COX}(u) Y_i^1(u) Z_i^{\otimes k} \exp(\beta^T Z_i), \text{ for } k = 0; 1; 2$$

$$E_{COX}(\beta; u) = \frac{S^{(1)}_{COX}(\beta; u)}{S^{(0)}_{COX}(\beta; u)}.$$

It has been shown that for given covariates X_i (Andersen & Gill, 1982),

$$G_C^{COX}(t;X_i) \quad G_C(t;X_i) \quad {}_p \quad G_C(t;X_i) \quad e^{\beta^T X_i} \quad \beta_{C0}(t) \quad e^{(\ {}_0^T X_i)} \quad {}_{C0}(t)$$

$$ {}_p \quad G_C^{COX}(t;X_i) \sum_j \omega_{COX;j}^C(t;X_i)$$

where

$$\omega_{COX;j}^C(t;X_i) = \beta(t;X_i)^T f I_C(b) g^{-1} \int_0^{\infty} f X_j \quad E_C(b;u) g d M_{COX;j}^C(u;j$$

Now, it follows that Equation (6.2) can be approximated by $\sum_i b_i^{COX}$, where

$$b_i^{COX} = \int_0^{\tau} Z_i \, E_{COX}\left(b_{COX}; u\right) w_i^{COX}(u) \, d\hat{M}_{COX;i}^1(u)$$

$$d\hat{M}_{COX;i}^1(t) = dN_i^1(t) - Y_i^1(t) \exp\left(b_{COX}^T Z_i\right) d\hat{b}_{10}^{COX}(t)$$

and for Equation (6.3), it follows that

$$\begin{aligned}
(6{:}3) \quad & \sum_i \int_0^{\tau} f Z_i \, E_{COX}(\beta_0; t) g^T w_i^{COX}(t) dM_i^1(t) I(T_i < t) \sum_j \left[W_{COX;j}^C(T_i; X_i) - \bar{W}_{COX;j}^C(t; X_i) \right] \\
& \sum_i \sum_j \int_0^{\tau} Z_j \, E_{COX}(b_{COX}; t) \left[W_{COX;i}^C(T_j; X_j) - \bar{W}_{COX;i}^C(t; X_j) \right]^T \\
& \quad I(T_j < t) w_j^{COX}(t) d\hat{M}_{COX;j}^1(t) \\
= & \sum_i b_i^{COX}
\end{aligned}$$

Thus,

$$\begin{aligned}
\sqrt{n}\left(b_{COX} - \beta_0\right) = & \sqrt{n} I_{COX}\left(b_{COX}\right)^{-1} U_{COX}(\beta_0) \\
& \sqrt{n} I_{COX}\left(b_{COX}\right)^{-1} \sum_i b_i^{COX} + b_i^{COX}
\end{aligned}$$

where b_i^{COX} is the major term in the variance estimation. Next,

$$\sqrt{n}\left(\hat{\beta}_{10}^{COX}(t) - \beta_{10}(t)\right) = \sqrt{n}\int_0^t \left\{ \frac{\sum_i w_i^{COX}(u)dN_i^1(u)}{S_{COX}^{(0)}\left(\hat{\beta}_{COX}, u\right)} - \frac{\sum_i w_i^{COX}(u)dN_i^1(u)}{S_{COX}^{(0)}\left(\beta_0, u\right)} \right\} + \sqrt{n}\int_0^t \left(\frac{\sum_i w_i^{COX}(u)dN_i^1(u)}{S_{COX}^{(0)}\left(\beta_0, u\right)} - d\beta_{10}(u) \right)$$

$$\stackrel{p}{\to} \sqrt{n}\int_0^t E_{COX}\left(\beta_0, u\right)^T \frac{\sum_i w_i^{COX}(u)dN_i^1(u)}{S_{COX}^{(0)}\left(\beta_0, u\right)} - b_{COX} \quad 0$$

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Table 1: Simulation results for bias reduction with a single binary covariate (= 1).

Table 2: Simulation results for biases using 1 binary and 1 continuous covariate ($_1$ = 1; $_2$ = 0:5).

				Unadjusted weight				Cox model adjusted weight			
Scenario	N	Cens.		Bias (Std-B)	b(SD)	Coverage	MSE	Bias (Std-B)	b(SD)	Coverage	MSE
1	100	30%	$_1$	0.0148 (0.0521)	0.2793 (0.2849)	0.9462	0.0814	0.0154 (0.0542)	0.2793 (0.2847)	0.9463	0.0813
			$_2$	0.0130 (0.0873)	0.1424 (0.1483)	0.9381	0.0222	0.0130 (0.0876)	0.1424 (0.1482)	0.9394	0.0221
		50%	$_1$	0.0293 (0.0847)	0.3353 (0.3463)	0.9474	0.1207	0.0299 (0.0863)	0.3355 (0.3464)	0.9468	0.1209
			$_2$	0.0143 (0.0812)	0.1676 (0.1763)	0.9362	0.0313	0.0146 (0.0827)	0.1676 (0.1764)	0.9362	0.0313
	300	30%	$_1$	0.0039 (0.0242)	0.1595 (0.1608)	0.9498	0.0259	0.0041 (0.0254)	0.1592 (0.1602)	0.9495	0.0257
			$_2$	0.0042 (0.0521)	0.0807 (0.0813)	0.9494	0.0066	0.0043 (0.0535)	0.0806 (0.0811)	0.9485	0.0066
		5%0	$_1$	0.0062 (0.0327)	0.1898 (0.1883)	0.9525	0.0355	0.0063 (0.0333)	0.1897 (0.1881)	0.9529	0.0354
			$_2$	0.0063 (0.0661)	0.0941 (0.0958)	0.9448	0.0092	0.0065 (0.0674)	0.0941 (0.0957)	0.9438	0.0092
2	100	30%	$_1$	:0938 (0.2949)	0.3036 (0.3180)	0.9243	0.1099	0.0119 (0.0370)	0.3101 (0.3220)	0.9421	0.1038
			$_2$	0.0273 (0.1778)	0.1462 (0.1536)	0.9355	0.0243	0.0160 (0.1037)	0.1468 (0.1540)	0.9357	0.0240
		50%	$_1$	:0955 (0.2241)	0.4031 (0.4262)	0.9325	0.1908	0.0179 (0.0409)	0.4181 (0.4385)	0.9414	0.1926
			$_2$	0.0247 (0.1349)	0.1740 (0.1831)	0.9333	0.0341	0.0142 (0.0771)	0.1748 (0.1839)	0.9354	0.0340
	300	30%	$_1$	:1089 (0.6286)	0.1734 (0.1733)	0.9002	0.0419	0.0049 (0.0277)	0.1771 (0.1769)	0.9514	0.0313
			$_2$								

Table 3: Fit a proportional subdistribution hazards model.

	Unadjusted weight	Cox model adjusted weight
Variable	^; exp( ) (95% CI); P	^; exp( ) (95% CI); P
RELAPSE		
GP	0.38; 1.47(1.16-1.86); 0.0017	0.54; 1.71(1.34-2.20); < 0:0001
DNR	0.39; 1.48(1.18-1.86); 0.0007	0.35; 1.42(1.13-1.78); 0:0027
PREAUTO	0.41; 1.51(1.19-1.91); 0.0007	0.42; 1.53(1.21-1.93); 0:0004
TRM		
GP	0:59; 0.55(0.42-0.73); < 0:0001	0:56; 0.57(0.43-0.75); < 0:0001
DNR	0.57; 1.76(1.38-2.25); < 0:0001	0.55; 1.73(1.35-2.20); < 0:0001
PREAUTO	0:38; 0.68(0.51-0.91); 0.0099	0:37; 0.69(0.52-0.92); 0:0117

Table 4: Predicted CIF of relapse and TRM for a patient who received an HLA-identical sibling donor and allogeneic along transplantation

	Unadjusted Weight			Cox model adjusted Weight		
	1995-2000	2001-2005		1995-2000	2001-2005	
Time	$\hat{F}_1$ (95% CI)	$\hat{F}_2$ (95% CI)	$\|\hat{F}_1 \quad \hat{F}_2\|$	$\hat{F}_1$ (95% CI)	$\hat{F}_2$ (95% CI)	$\|\hat{F}_1 \quad \hat{F}_2\|$
RELAPSE						
1 Year	0.16 (0.13-0.19)	0.23 (0.18-0.27)	0.07	0.15 (0.13-0.17)	0.24 (0.18-0.30)	0.09
3 Year	0.25 (0.20-0.29)	0.34 (0.28-0.40)	0.09	0.22 (0.20-0.25)	0.35 (0.28-0.42)	0.13
5 Year	0.29 (0.24-0.34)	0.40 (0.33-0.46)	0.11	0.26 (0.24-0.30)	0.41 (0.33-0.49)	0.15
TRM						
1 Year	0.38 (0.32-0.43)	0.23 (0.18-0.28)	0.15	0.37 (0.34-0.41)	0.23 (0.17-0.29)	0.14
3 Year	0.42 (0.37-0.48)	0.26 (0.20-0.32)	0.16	0.42 (0.38-0.46)	0.27 (0.20-0.33)	0.15
5 Year	0.44 (0.38-0.49)	0.27 (0.21-0.33)	0.17	0.43 (0.39-0.47)	0.27 (0.21-0.34)	0.16

Figure 1: Simulation results (1 covariate) for biases of cumulative baseline subdistribution hazards at $t = (0{:}25; 0{:}5; 0{:}75; 1)^T$.

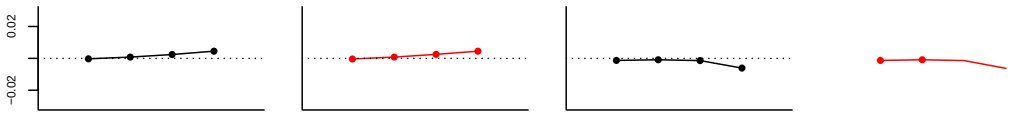
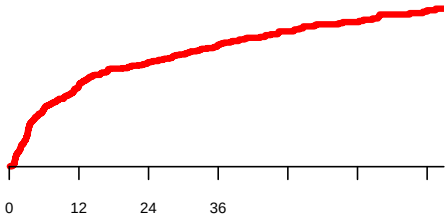


Figure 2: Simulation results (2 covariates) for biases of cumulative baseline subdistribution hazards at $t = (0{:}25; 0{:}5; 0{:}75; 1{:}00)^T$.


0
12
24
36