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Methods for Contrasting Gap Time Hazard Functions: Application to Repeat Liver Transplantation

Xu Shu¹ and Douglas E. Schaebel²

¹Novartis Pharmaceuticals, One Health Plaza, East Hanover, NJ 07936, USA

²Department of Biostatistics, University of Michigan, 1415 Washington Heights, Ann Arbor, MI 48109-2029, USA

Abstract

In studies featuring a sequence of ordered events, gap times between successive events are often of interest. Despite the rich literature in this area, very few methods for comparing gap times have been developed. We propose methods for estimating a hazard ratio connecting the first and second gap times. Specifically, a two-stage procedure is developed based on estimating equations. At the first stage, a proportional hazards model is fitted for the first gap time. Weighted estimating equations are then solved at the second stage to estimate the hazard ratio between the first and second gap times. The proposed estimator has a closed form and, being analogous to a standardized mortality ratio, is easy to interpret. Large sample properties of the proposed estimators are derived, with simulation studies used to evaluate finite sample characteristics. Extension of the approach to accommodate a piecewise constant hazard ratio is considered. The proposed methods are applied to contrast repeat (second) versus primary (first) liver transplants with respect to graft failure, based on national registry data.

Keywords

Counting processes; Inverse weighting; Organ transplantation; Proportional hazards model; Semiparametric methods; Survival analysis

1 Introduction

In clinical and biomedical studies, multiple event data are encountered often. Examples include the scenario where one person experiences a series of events, such as numbered hospitalizations. In this report, we are interested in the gap times, i.e., times between successive events. An alternative time scale for such data would be the time from the time of origin to whenever the event occurs, known as the total time. However, gap times are typically of more direct interest compared to total times, depending on the specific application. For example, a person who just received surgery to remove a cancerous tumor may wonder when s/he will experience a tumor recurrence. Such questions are more readily addressed through a gap time scale.

Gap time analysis has been an active area of methodological research in recent years, partly because of its broad applicability to various fields. There are two major challenges in analyzing gap time data. The first challenge is non-identifiability [1–4]. In particular, because the support of the first gap time is usually not contained within the support of the censoring distribution, not all first gap times are observed. As a result, the marginal distributions of the second and subsequent gap times cannot be identified without parametric assumptions; except in the setting wherein the within-subject gap times are mutually independent, which is an unrealistic assumption in most real-data applications. The second challenge is induced dependent censoring [2,5,6]. For example, with a longer first gap time, the second gap time is more likely to be censored. Therefore, given that the gap times are typically correlated, the second and subsequent gap times will depend on the censoring variables, which violates the fundamental assumption of independent censoring.

Various methods have been proposed for gap time analysis. These existing methods can be broadly categorized into either those that estimate the joint/conditional survival functions non-parametrically, or those which incorporate the covariate effects on the gap time hazard functions semi-parametrically. The former category of methods includes those proposed by Visser [6], Wang and Wells [7], Lin et al. [2], Wang and Chang [8], Peña et al. [9], van der Laan et al. [10], Schaubel and Cai [3], and Andrei and Murray [11]. For the latter category, Prentice et al. [12] assumed that the within-subject gap times are independent, and developed hazard models for each of the total and gap time scales. Huang [5] developed regression methods for gap times based on the accelerated failure time model. Huang and Chen [13] proposed a marginal proportional hazards model, when there are random effects leading to intra-subject correlation. Schaubel and Cai [14] proposed gap time regression methods for the hazard functions based on stratified proportional hazards models. Chen et al. [15] proposed stratified proportional reverse-time hazard models, where a longitudinal pattern parameter can be estimated to compare gap times. However, a monotone time trend is required in the modeling; plus, the individual baseline hazard functions are sometimes not identifiable. Strawderman [16] generalized the accelerated failure time model for gap times via conditional semiparametric intensity modeling. The model was later extended to handle correlated gap times by incorporating a multiplicative gamma frailty [17]. Huang and Liu [18] proposed a joint frailty model which could model disease recurrences and survival at the same time. Clement and Strawderman [19] developed modified generalized estimating equations to estimate parameters associated with the conditional gap time means and variances. Du et al. [20] estimated the gap time hazard non-parametrically by building a smoothing spline ANOVA frailty model.

Very few of the above-listed methods could be readily applied to compare gap times. Those that could be used to compare gap times were not developed for this purpose and, as a result, contrast gap times through rather strict assumptions, such as independence of gap times for the same subject. In this report, we propose novel methods for estimating a hazard ratio for contrasting the first and second gap time hazard functions. We avoid assuming independence of within-subject gap times from two perspectives: first, by explicitly acknowledging their dependence in the model formulation, and second, by not attempting inference on a (generally non-identifiable) marginal quantify through equating it to a (typically estimable) conditional quantity.

The motivating example for the proposed methods is in the context of liver transplantation. For patients with end-stage liver disease and acute liver failure, liver transplantation is the preferred treatment. Retransplantation may occur if the transplanted liver fails. However, there are many more (i.e., thousands more) patients on the wait-list compared to the number of donor organs available. Thus, it is extremely important to pursue an organ allocation policy that makes the best use of limited organs. Current policy uses the Model for End-Stage Liver Disease (MELD) score to determine a patient's ranking on the wait-list. The score is composed of serum creatinine, serum bilirubin, and international normalized ratio for prothrombin time (INR). The MELD score serves to reflect the mortality rate to which a patient is subject in the absence of liver transplantation. The current liver allocation rules do not take into account whether a patient would be a primary (i.e., first-time) liver transplant recipient, or s/he has already had a liver transplant and, hence, is a repeat-transplant candidate. This motivates us to compare primary and repeat (in particular, second) liver transplantation with respect to graft survival. Results of the analysis are important to the liver transplant community from a public health perspective. For example, a finding that graft survival after the first transplant is significantly better than the after repeat transplantation might provide some new insights into how to assign the limited organs efficiently and fairly. It has been consistently reported that the outcomes of the repeat liver transplantation are inferior to those of the first transplantation [21–27]. The most common approach for comparing first and second transplants has been to compare Kaplan–Meier curves. However, the afore-described issues of non-identifiability and dependent censoring were generally ignored, which could greatly bias the comparison.

In this report, we propose methods for estimating the marginal hazard ratio contrasting the first and second gap times. Specifically, a two-stage procedure is developed based on estimating equations. At the first stage, a proportional hazards model is fitted for the first gap time. Weighted estimating equations are then solved at the second stage to estimate the hazard ratio between the first and second gap times. The proposed estimator is intuitive and has a closed form. Rather than fitting a regression model to the second gap times, the second gap time counting process (a weighted version thereof) is used directly. The handling of the second gap time does not require additional assumptions regarding the between-gap-time association, but does in turn place restrictions on the range of the observed data that can be utilized (similar to various existing methods). For the case where the gap time hazard functions are non-proportional, we develop an extension of proposed methods which allows the gap time hazard ratio to be piecewise constant.

The remainder of the report is organized as follows. In Sect. 2, we describe the notation and methods. Asymptotic results are provided in Sect. 3. Simulation studies are carried out in Sect. 4 to demonstrate the performance of the estimators in finite samples. In Sect. 5, extension of the methods through a piecewise constant hazard ratio is provided. We apply the proposed methods to national liver transplant data in Sect. 6. A discussion is given in Sect. 7.

2 Proposed Methods

First, we introduce the necessary notation. Subject is denoted by $i = 1, \dots, n$. For ease of presentation, we only consider the case of comparing two gap times. Suppose that T_{ij} are the total times of the events ($j = 1, 2$), such that T_{i1} is also the first gap time and $\tilde{T}_{i2} = T_{i2} - T_{i1}$ is the second gap time. The censoring variable is C_i such that the first gap time is potentially censored by C_i and the second gap time is potentially censored by $\tilde{C}_{i2} = C_i - T_{i1}$. The covariate vector for subject i is given by $\mathbf{Z}_i$. We define $\tau = \sup\{t: P(C_i \geq t) > 0\}$.

Due to the afore-listed non-identifiability issues, we choose to work with the following hazard functions,

$$\begin{aligned}\lambda_{i1}(t) &= \lim_{\delta \rightarrow 0} \delta^{-1} P(t < T_{i1} \leq t + \delta | T_{i1} \geq t) \\ \lambda_{i2}(t; t_1) &= \lim_{\delta \rightarrow 0} \delta^{-1} P(t < \tilde{T}_{i2} \leq t + \delta | \tilde{T}_{i2} \geq t, T_{i1} \leq t_1),\end{aligned}$$

noting that the conditional distribution of $\{\tilde{T}_{i2} | T_{i1} \leq t_1\}$, including the hazard function $\lambda_{i2}(t; t_1)$, is identifiable for (t, t_1) such that $t + t_1 \leq \tau$ [2]. We assume that the gap time hazard functions are proportional, i.e.,

$$\lambda_{i2}(t; t_1) = \lambda_{i1}(t) e^{\theta_0}. \quad (1)$$

Note that (1) involves contrasting a conditional hazard function of $\tilde{T}_{i2}$ with a marginal hazard function of T_{i1} . This should be viewed with at least the following considerations in mind. First, since the marginal distribution of $\tilde{T}_{i2}$ is not identifiable, there is little motivation for using it in a comparison of gap times. Second, the $\tilde{T}_{i2}$ observed in practice are essentially subject to the same constraint (i.e., conditionality on a range of T_{i1} , whether intended or not). Third, the contrast is between the second gap time hazard (i.e., identifiable version thereof) and the hazard function that would apply if in fact the subject were ‘fresh,’ in which case the first gap time hazard would apply. Note that, the fact that we model the hazard of $\tilde{T}_{i2} | T_{i1} \leq t_1$, without equating this hazard to the marginal hazard of $\tilde{T}_{i2}$ implies that $\tilde{T}_{i2}$ and T_{i1} are not assumed independent. Note also that not specifying the functional nature of the association between $\tilde{T}_{i2} | T_{i1} \leq t_1$ and T_{i1} does not imply their independence (per the related idea of marginally modeling correlated failure times, e.g., [28]).

The counting and at-risk processes are defined as,

$$N_{i1}(t) = I(T_{i1} \wedge C_i \leq t, T_{i1} \leq C_i) \quad (2)$$

$$Y_{i1}(t) = I(T_{i1} \wedge C_i \geq t) \quad (3)$$

$$N_{i2}(t; t_1) = I(\tilde{T}_{i2} \wedge \tilde{C}_i \leq t, \tilde{T}_{i2} \leq \tilde{C}_i, T_{i1} \leq t_1) \quad (4)$$

$$Y_{i2}(t; t_1) = I(\tilde{T}_{i2} \wedge \tilde{C}_i \geq t, T_{i1} \leq t_1). \quad (5)$$

Integrating and compensating produces the error terms,

$$\begin{aligned} M_{i1}(t) &= N_{i1}(t) - \int_0^t Y_{i1}(s) \Lambda_{i1}(ds) \\ M_{i2}(t; t_1) &= N_{i2}(t; t_1) - \int_0^t Y_{i2}(s; t_1) \Lambda_{i2}(ds; t_1), \end{aligned}$$

where $\Lambda_{i1}(t) = \int_0^t \lambda_{i1}(ds)$ and $\Lambda_{i2}(t; t_1) = \int_0^t \lambda_{i2}(ds; t_1)$.

In order to estimate θ_0 , we propose to use a two-stage procedure. First, we model the hazard function of the first gap time with the following proportional hazards model:

$$\lambda_{i1}(t) = \lambda_0(t) \exp\{\beta'_0 \mathbf{Z}_i\}, \quad (6)$$

where $\lambda_0(t)$ is a baseline hazard function, and β_0 is a parameter vector. In the second stage, we solve the following weighted estimating equation,

$$\sum_{i=1}^n \int_0^{\tau_2} W_{i2}(s; t_1) M_{i2}(ds; t_1) = 0,$$

where we set $\tau_2 = \tau - t_1$ and define the weight function $W_{i2}(s, t_1) = Y_{i2}(s, t_1) P(C_i = s + T_{i1} | T_{i1})^{-1}$. Solving the above equation, we have the following working estimator of θ_0 ,

$$\log \left\{ \frac{\sum_{i=1}^n \int_0^{\tau_2} W_{i2}(s; t_1) N_{i2}(ds; t_1)}{\sum_{i=1}^n \int_0^{\tau_2} W_{i2}(s; t_1) \Lambda_{i1}(ds; t_1)} \right\}. \quad (7)$$

We refer to this as a working estimator since it applies when both $\Lambda_{i1}(t)$ and $W_{i2}(s, t_1)$ are known, which is practically never the case. As implied previously, we compute $\hat{\Lambda}_{i1}(t)$ using $\hat{\beta}$ and $\hat{\Lambda}_0(t)$ from an unweighted Cox regression applied to the first gap time. It remains to estimate $P(C_i = s + T_{i1} | T_{i1})$, and we do so semi-parametrically. Specifically, we allow C_i to depend on a vector of covariates $\mathbf{Z}_i^C$, and assume that the hazard of C_i follows a proportional hazards model,

$$\lambda_i^C(t) = \lambda_0^C(t) \exp\{\alpha_0' \mathbf{Z}_i^C\}.$$

As such, we have $\hat{P}(C_i > t | \mathbf{Z}_i^C) = \exp \left\{ - \int_0^t e^{\hat{\alpha}' \mathbf{Z}_i^C} d\hat{\Lambda}_0^C(u) \right\}$, with

$\hat{W}_{i2}(s; t_1) = Y_{i2}(s; t_1) \exp \left\{ \hat{\Lambda}_i^C(s + T_{i1}) \right\}$, where $\Lambda_i^C(t) = \int_0^t \lambda_i^C(u) du$. We discuss some implementation issues related to Inverse Probability of Censoring Weighting (IPCW) in Sect. 7.

Thus, we estimate θ_0 by,

$$\hat{\theta} = \log \left\{ \frac{\sum_{i=1}^n \int_0^{\tau_2} \hat{W}_{i2}(s; t_1) N_{i2}(ds; t_1)}{\sum_{i=1}^n \int_0^{\tau_2} \hat{W}_{i2}(s; t_1) \hat{\Lambda}_{i1}(ds; t_1)} \right\}. \quad (8)$$

To assess the proportionality assumption, one could contrast the first and second gap time hazards through $\hat{\theta}(t)$, computed by replacing τ_2 with t in the upper limit of the integrals in (8). In particular, lack of dependence of $\hat{\theta}(t)$ on t would imply proportionality.

3 Asymptotic Properties

We begin by defining the following quantities:

$$\begin{aligned} s_C^{(d)}(t, \alpha) &= E \left[Y_i^C(t) \mathbf{Z}_i^{C \otimes d} \exp \left\{ \alpha' \mathbf{Z}_i^C \right\} \right] \\ s_1^{(d)}(t, \beta) &= E \left[Y_{i1}(t) \mathbf{Z}_i^{\otimes d} \exp \left\{ \beta' \mathbf{Z}_i \right\} \right] \\ S_C^{(d)}(t, \alpha) &= n^{-1} \sum_{i=1}^n Y_i^C(t) \mathbf{Z}_i^{C \otimes d} \exp \left\{ \alpha' \mathbf{Z}_i^C \right\} \\ S_1^{(d)}(t, \beta) &= n^{-1} \sum_{i=1}^n Y_{i1}(t) \mathbf{Z}_i^{\otimes d} \exp \left\{ \beta' \mathbf{Z}_i \right\} \\ \bar{z}_C(t, \alpha) &= \frac{s_C^{(1)}(t, \alpha)}{s_C^{(0)}(t, \alpha)} \\ \bar{z}_1(t, \alpha) &= \frac{s_1^{(1)}(t, \alpha)}{s_1^{(0)}(t, \alpha)} \end{aligned}$$

for $d = 0, 1, 2$, where, for a vector $\mathbf{a}$, $\mathbf{a}^{\otimes 0} = 1$, $\mathbf{a}^{\otimes 1} = \mathbf{a}$, and $\mathbf{a}^{\otimes 2} = \mathbf{a}\mathbf{a}'$. The counting and at-risk processes of the censoring variable C_i are defined as,

$$\begin{aligned} N_i^C(t) &= I \left(C_i \leq T_{i1} + \tilde{T}_{i2}, C_i \leq t \right) \\ Y_i^C(t) &= I \left(C_i \wedge (T_{i1} + \tilde{T}_{i2}) \geq t \right), \end{aligned}$$

such that the corresponding Martingale is given by

$$M_i^C(t) = N_i^C(t) - \int_0^t Y_i^C(u) \lambda_i^C(u) du.$$

In order to derive the asymptotic properties for $\hat{\theta}$, we assume that the following regularity conditions hold for $i = 1, \dots, n$, $0 \leq t_1, 0 \leq u \leq \tau_2$:

- a. $\{N_{i1}(\cdot), N_{i2}(\cdot), Y_{i1}(\cdot), Y_{i2}(\cdot), \mathbf{Z}_i\}$ are independent and identically distributed;
- b. $E[Y_{i1}(s)] > 0$ and $E[Y_{i2}(u; t_1)] > 0$;
- c. Elements of $\mathbf{Z}_i$ and $\mathbf{Z}_i^C$ are bounded almost surely;
- d. $\Lambda_{01}(s) < \infty$ and $\Lambda_{02}(u, t_1) < \infty$;
- e. Positive-definiteness of the following matrices:

$$\begin{aligned} \sum_C(\boldsymbol{\alpha}) &= E \left[\int_0^\tau \left\{ \frac{\mathbf{s}_C^{(2)}(t, \boldsymbol{\alpha})}{\mathbf{s}_C^{(0)}(t, \boldsymbol{\alpha})} - \bar{\mathbf{z}}_C(t, \boldsymbol{\alpha})^{\otimes 2} \right\} dN_i^C(t) \right], \\ \sum_C(\boldsymbol{\beta}) &= E \left[\int_0^\tau \left\{ \frac{\mathbf{s}_1^{(2)}(t, \boldsymbol{\beta})}{\mathbf{s}_1^{(0)}(t, \boldsymbol{\beta})} - \bar{\mathbf{z}}_1(t, \boldsymbol{\beta})^{\otimes 2} \right\} dN_{i1}(t) \right]. \end{aligned}$$

The essential asymptotic properties are summarized by the following theorem, a proof of which is provided in the Supplementary Materials.

Theorem 1

Under conditions (a) to (e), we have the following linear representations pertinent to the proposed estimator,

$$n^{1/2}(\hat{\theta} - \theta_0) = n^{-1/2} \sum_{i=1}^n \phi_i(\tau_2) + o_p(1),$$

where $\phi_i(\tau_2)$ ($i = 1, \dots, n$) are independent and identically distributed mean-zero random variables, such that $E\{\phi_i(\tau_2)^2\} < \infty$. Thus, $n^{1/2}(\hat{\theta} - \theta_0)$ is asymptotically normal with mean 0 and variance $E\{\phi_i(\tau_2)^2\}$, with

$$\phi_i(t) = e^{-\theta_0} \left\{ \frac{1}{B(t)} \varphi_{i1}(t) - \frac{A(t)}{B(t)^2} \varphi_{i2}(t) \right\},$$

where

$$\begin{aligned} A(t) &= \int_0^t E \left[W_{i2}(s; t_1) \exp \left\{ \boldsymbol{\beta}'_0 \mathbf{Z}_i \right\} \right] \Lambda_{02}(ds; t_1) \\ B(t) &= \int_0^t E \left[W_{i2}(s; t_1) \exp \left\{ \boldsymbol{\beta}'_0 \mathbf{Z}_i \right\} \right] \Lambda_{01}(ds), \end{aligned}$$

and with

$$\begin{aligned} \varphi_{i1}(t) &= \int_0^t E \left[W_{j2}(s) \mathbf{k}'_{jC}(s + T_{j1}; \boldsymbol{\alpha}_0) N_{j2}(ds; t_1) \right] \sum_C(\boldsymbol{\alpha}_0)^{-1} \mathbf{U}_i^C(\boldsymbol{\alpha}_0) \\ &\quad + \int_0^t \int_{u-T_{j1}}^t E \left[W_{j2}(s) \exp \left\{ \boldsymbol{\alpha}'_0 \mathbf{Z}_j^C \right\} N_{j2}(ds; t_1) \right] \mathbf{s}_C^{(0)}(u; \boldsymbol{\alpha}_0)^{-1} dM_i^C(u; \boldsymbol{\alpha}_0) \\ &\quad + \int_0^t W_{i2}(s; t_1) M_{i2}(ds; t_1) \end{aligned}$$

$$\begin{aligned}
\varphi_{i2}(t) = & \int_0^t E \left[W_{j2}(s) \mathbf{k}'_{jC}(s+T_{j1}; \boldsymbol{\alpha}_0) \Lambda_{j1}(ds) \right] \sum_C (\boldsymbol{\alpha}_0)^{-1} \mathbf{U}_i^C(\boldsymbol{\alpha}_0) \\
& + \int_0^t \int_{u-T_{j1}}^t E \left[W_{j2}(s) \exp \left\{ \boldsymbol{\beta}'_0 \mathbf{Z}_j \right\} \Lambda_{j1}(ds) \right] s_C^{(0)}(u; \boldsymbol{\alpha}_0)^{-1} dM_i^C(u; \boldsymbol{\alpha}_0) \\
& + \int_0^t E \left[W_{j2}(s; t_1) \exp \left\{ \boldsymbol{\beta}'_0 \mathbf{Z}_j \right\} (\mathbf{Z}_j - \bar{z}_1(s; \boldsymbol{\beta}_0))' \Lambda_{01}(ds) \right] \\
& \quad \times \sum_1 (\boldsymbol{\beta}_0)^{-1} \mathbf{U}_{i1}(\boldsymbol{\beta}_0) \\
& + \int_0^t E \left[W_{j2}(s; t_1) \exp \left\{ \boldsymbol{\beta}'_0 \mathbf{Z}_j \right\} \right] s_1^{(0)}(s; \boldsymbol{\beta}_0)^{-1} dM_{i1}(s; \boldsymbol{\beta}_0),
\end{aligned}$$

where we define

$$\begin{aligned}
\mathbf{k}_{jC}(t; \boldsymbol{\alpha}) &= \exp \left\{ \boldsymbol{\alpha}' \mathbf{Z}_j^C \right\} \int_0^t \left\{ \mathbf{Z}_j^C - \bar{z}_C(u; \boldsymbol{\alpha}) \right\} \lambda_0^C(u) du \\
\mathbf{U}_i^C(\boldsymbol{\alpha}) &= \int_0^\tau \left\{ \mathbf{Z}_i^C - \bar{z}_C(t; \boldsymbol{\alpha}) \right\} dM_i^C(t; \boldsymbol{\alpha}) \\
\mathbf{U}_{i1}(\boldsymbol{\beta}) &= \int_0^\tau \left\{ \mathbf{Z}_i - \bar{z}_1(t; \boldsymbol{\beta}) \right\} dM_{i1}(t; \boldsymbol{\beta}).
\end{aligned}$$

The asymptotic linear representation follows from the large-sample results of [29].

Consistent estimator of the asymptotic variance is given by $n^{-2} \sum_{i=1}^n \hat{\phi}_i(\tau_2)^2$, which is written out in the Supplementary Materials in Appendix B.

4 Simulations

For each subject, we generated two covariates, Z_{i1} and Z_{i2} , which were independent Bernoulli(0.5) variables. Our objective is to simulate the first and second gap times from the following two proportional hazards models:

$$\begin{aligned}
P(T_{i1} > t | \mathbf{Z}_i) &= \exp \left[-\lambda_0 t \exp \left\{ \boldsymbol{\beta}'_0 \mathbf{Z}_i \right\} \right] \\
P(\tilde{T}_{i2} > t | \mathbf{Z}_i, T_{i1} \leq t_1) &= \exp \left[-\lambda_0 t \exp \left\{ \boldsymbol{\beta}'_0 \mathbf{Z}_i + \theta_0 \right\} \right],
\end{aligned}$$

such that T_{i1} is correlated with $\tilde{T}_{i2}$ given $\mathbf{Z}_i = \{Z_{i1}, Z_{i2}\}'$.

The core idea we used to simulate two correlated variables is to generate two correlated uniformly distributed random variables first, and then use them to invert the targeted survival functions. In order to simulate two correlated uniformly distributed random variables, we generate variables following a bivariate normal distribution with a correlation coefficient ρ , so that the marginal survival functions would both be Uniform(0,1). This idea is to generate a marginal distribution (for T_{i1}) and a conditional distribution (for $\tilde{T}_{i2}$) which are correlated above and beyond the mutual association with $\mathbf{Z}_i$.

Since the target distribution for $\tilde{T}_{i2}$ is conditioning on $(T_{i1} \leq t_1)$, we first generated $I(T_{i1} \leq t_1)$ for $i = 1, \dots, n$ from a Bernoulli distribution with probability

$$P(T_{i1} \leq t_1 | \mathbf{Z}_i) = 1 - \exp \left[-\lambda_0 t_1 \exp \left\{ \boldsymbol{\beta}'_0 \mathbf{Z}_i \right\} \right].$$

For subjects with $T_{i1} \leq t_1$, we generated correlated $[T_{i1}|Z_i]$ and $[\tilde{T}_{i1}|Z_i, T_{i1} \leq t_1]$ by first generating $(\mathcal{E}_{i1}, \mathcal{E}_{i2})$ from a bivariate normal distribution with $E[\mathcal{E}_{i1}] = E[\mathcal{E}_{i2}] = 0$, $V(\mathcal{E}_{i1}) = V(\mathcal{E}_{i2}) = 1$ and $\text{corr}(\mathcal{E}_{i1}, \mathcal{E}_{i2}) = \rho$. Denoting the marginal cumulative distribution functions for $\mathcal{E}_{i1}$ and $\mathcal{E}_{i2}$ by $\Phi_1(\cdot)$ and $\Phi_2(\cdot)$, respectively, $U_{i1} = \Phi_1(\mathcal{E}_{i1})$ and $U_{i2} = \Phi_2(\mathcal{E}_{i2})$ will be correlated random variables, with Uniform(0,1) marginals. Next, U_{i1} and U_{i2} are used to invert the following two equations,

$$P(T_{i1} > t | Z_i, T_{i1} \leq t_1) = \frac{\exp[-\lambda_0 t \exp\{\beta'_0 Z_i\}] - \exp[\lambda_0 t_1 \exp\{\beta'_0 Z_i\}]}{1 - \exp[-\lambda_0 t_1 \exp\{\beta'_0 Z_i\}]}$$

$$P(\tilde{T}_{i2} > t | Z_i, T_{i1} \leq t_1) = \exp[-\lambda_0 t \exp\{\beta'_0 Z_i + \theta_0\}],$$

to generate T_{i1} and $\tilde{T}_{i2}$, respectively. Note that the above $P(T_{i1} > t | Z_i, T_{i1} \leq t_1)$ subjects with $T_{i1} > t_1$, we simulate the first and second gap times from

$$P(T_{i1} > t | Z_i, T_{i1} > t_1) = \frac{\exp[-\lambda_0 t \exp\{\beta'_0 Z_i\}]}{\exp[-\lambda_0 t_1 \exp\{\beta'_0 Z_i\}]} \quad (9)$$

$$P(\tilde{T}_{i2} > t | Z_i, T_{i1} > t_1) = \exp\{-\lambda_0 t \exp\{\beta'_0 Z_i + \theta_0\}\} \quad (10)$$

The hazard function of the censoring variable, C_i , followed a proportional hazards model

$$P(C_i > t | Z_i) = \exp[-\lambda_0^C t \exp\{\alpha'_0 Z_i^C\}].$$

Initially, we set the parameters $\beta_1 = \log(1.5)$, $\beta_2 = -\log(1.5)$, and $\theta_0 = 0.5$, with baseline hazard $\lambda_0 = 0.6$ and correlation $\rho = 0.5$. With respect to the censoring distribution, we set $\lambda_0^C = 0.2$, $\alpha_1 = 0.2$, $\alpha_2 = -0.2$ (Table 1, Setting B), and capped follow-up at $\tau = 10$. We set $t_1 = 3$. Under this data configuration, $P(T_{i1} \leq t_1) \approx 0.83$. The correlation between T_{i1} and $\tilde{T}_{i2}$ conditioning on $\{T_{i1} \leq t_1\}$ equals 0.47. There are approximately 25% first gap times being censored and, in subjects with $\{T_{i1} \leq t_1\}$, approximately 30% of the second gap times are censored. Additional scenarios were also simulated; one with weaker correlation (Setting A: $\rho = 0.3$), and another with stronger correlation (Setting C: $\rho = 0.7$). Settings with heavier censoring were also evaluated, setting $\lambda_0^C = 0.3$; this results in approximately 33% censored first gap times, and 41% censored gap times in subjects with $\{T_{i1} \leq t_1\}$. Under this heavy censoring scenario, three correlation coefficients are used: $\rho = 0.3, 0.5$, and 0.7 (Settings D, E, and F, respectively). Table 1 lists all six parameter settings, with the corresponding results summarized in Table 2.

We simulated $n = 250$ subjects and ran 1000 replicates for each data configuration, with the estimated $\hat{\theta}(t)$ evaluated at three time points $t = 1$, $t = 2$, and $t = 3$. Table 2 lists the results

from the simulation. The biases are very close to zero for each time point we evaluated. The empirical standard deviations (ESDs) and the averaged asymptotic standard errors (ASEs) match very well across all time points, such that empirical 95% coverage probability is approximately 0.95. It is noteworthy that when the correlation between gap times, ρ , increases, the ESD of the estimator decreases. It is also interesting that ESD does not decrease monotonically with increasing t . Basically, the increase in event total associated with increasing t arises at the price of tail instability likely exacerbated by the weight function (and its concomitant increasing variance).

To evaluate the performance of the proposed methods in smaller samples, we cut the sample size in half (such that $n = 125$), and re-ran the above-listed configurations. As demonstrated by Table 3, the proposed estimator remains approximately unbiased, with the ASE closely approximating the ESD. Note that the weight function was capped by the 97.5th percentile.

Overall, the results indicate that the estimator works well under the scenarios we considered. In addition, the asymptotic variance estimator appears to be quite accurate in estimating the standard errors, at least in reasonable-sized samples.

Finally, we examined simulations which examine a naive analysis; in this case, it based on a Cox model fitted to stacked first and second gap time data, with no inverse weighting to eliminate induced dependent censoring, and with no range restrictions to address identifiability issues. As shown in Table 4, results indicate that such a method performs quite poorly in terms of bias in the point estimator and asymptotic variance.

5 Extension to Piecewise Constant Hazard Ratio

In many practical settings, the contrast between gap time hazard functions will not be constant over follow-up time. In such cases, a more reasonable model than (1) would be given, in very general terms, by $\lambda_{i2}(t; t_1) = \lambda_{i1}(t) e^{\theta_0(t)}$. As a compromise between fully parameterizing $\theta_0(t)$ and estimating the time-varying hazard ratio non-parametrically we propose estimating a piecewise constant contrast between gap time hazard functions. Specifically, one would subdivide the follow-up interval $(0, \tau_2]$ into K subintervals, $(s_{k-1}, s_k]$, for $k = 1, \dots, K$, with $s_0 \equiv 0$ and $s_K \equiv \tau_2$. The model for the second gap time hazard would then be given by

$$\lambda_{i2}(t; t_1) = \lambda_{i1}(t) e^{\theta_k} \quad t \in (s_{k-1}, s_k], \quad (11)$$

with the same model, given by (6), assumed for the first gap time.

Through steps that parallel the progression from (1) to (8), θ_k from (11) can be estimated by

$$\hat{\theta}_k = \log \left\{ \frac{\sum_{i=1}^n \int_{s_{k-1}}^{s_k} \hat{W}_{i2}(s; t_1) N_{i2}(ds; t_1)}{\sum_{i=1}^n \int_{s_{k-1}}^{s_k} \hat{W}_{i2}(s; t_1) \hat{\Lambda}_{i1}(ds; t_1)} \right\}. \quad (12)$$

Asymptotic properties follow directly from Theorem 1. In particular,

$$n^{1/2}(\widehat{\theta}_k - \theta_k) = n^{-1/2} \sum_{i=1}^n \phi_{ik} + o_p(1), \text{ where}$$

$$\phi_{ik} = e^{-\theta_k} \left\{ \frac{1}{B_k} \varphi_{ik1} - \frac{A_k}{B_k^2} \varphi_{ik2} \right\},$$

where we define

$$A_k = \int_{s_{k-1}}^{s_k} E \left[W_{i2}(s; t_1) \exp \left\{ \beta'_0 \mathbf{Z}_i \right\} \right] \Lambda_{02}(ds; t_1) \\ B_k = \int_{s_{k-1}}^{s_k} E \left[W_{i2}(s; t_1) \exp \left\{ \beta'_0 \mathbf{Z}_i \right\} \right] \Lambda_{01}(ds),$$

and, analogously, with φ_{ik1} and φ_{ik2} defined as their counterparts, $\varphi_{i1}(t)$ and $\varphi_{i2}(t)$ but with $(0, t]$ replaced by $(s_{k-1}, s_k]$ for the integration.

Various techniques could be employed to select the number and position of the cut points.

Given that each $\exp\{\widehat{\theta}_k\}$ is explicitly computed as a ratio of integrals, one would want to ensure there are enough events in each subinterval to lead to sufficiently precise estimation. In most cases, it should suffice to have 10 events per subinterval, for each of the first and second gap times. For example, quintiles (or perhaps deciles, given sufficient data) for the observed events times could serve as initial choices for the break points. It may be desirable to replace these initial break points with similar round numbers, in the interests of clinical relevance, e.g., choose 2 months, rather than 2.06 months. Estimation could then be carried out for each subinterval, with adjacent subintervals perhaps subsequently pooled when approximately equal. Another option would be to compute and plot $\widehat{\theta}(t)$ from Sect. 2 for various values of t , then identify (e.g., through visual inspection) subintervals of t within which $\widehat{\theta}(t)$ was approximately constant.

Note that both $\widehat{\theta}(t)$ and the piecewise approach described in this section address non-proportional gap time hazards. In practice, the two approaches would best be used in tandem. For instance, $\widehat{\theta}(t)$ accumulates information over $(0, t]$, such that a grid of t values can be chosen quickly without much need to run preliminary descriptive analysis. If non-proportionality is present, then it will be identified by a trend in $\widehat{\theta}(t)$ with increasing t . That said, $\widehat{\theta}(t)$ represents an average HR over t that is difficult to interpret and depends on the censoring distribution. Therefore, in situations where non-proportionality is present, it would typically be preferable to then estimate a piecewise constant hazard ratio. We illustrate this type of approach in Sect. 6.

6 Application to Liver Transplant Data

In this section, we first describe the observed data and the objectives addressed by our analysis. We then outline the regression modeling and subsequent contrasting of the first and second gap time hazards. The subsequent subsection describes the analysis assuming a

piecewise constant hazard ratio. The section concludes with some additional analysis examining adherence of the data to the modeling assumptions, as well as the application of ‘naive’ methods which, by failing to consider the specifics of the data structure, could be expected to yield biased results.

6.1 Data and Objectives

We applied the proposed methods to liver transplant data obtained from the Scientific Registry of Transplant Recipients (SRTR). The SRTR data system includes data on all donor, wait-listed candidates, and transplant recipients in the U.S., submitted by the members of the Organ Procurement and Transplantation Network (OPTN), and has been described elsewhere. The Health Resources and Services Administration (HRSA), U.S. Department of Health and Human Services provides oversight to the activities of the OPTN and SRTR contractors.

Our objective is to contrast the graft failure hazard functions for first and second liver transplants. Graft survival is defined as survival with a functioning graft. Thus, the earliest of transplant failure or death is considered to be the event time. We included adult patients (age 18) that received their first liver transplant between March 1, 2002 and December 31, 2012. Living-donor transplants, transplants to status 1 (acute liver failure) patients, and patients with a MELD exception score were excluded. The end of observation period was December 31, 2012, since death information after that date was possibly incomplete.

In the final dataset, we have 31,914 subjects. There are 31,914 primary liver transplants, and 1566 second transplants. Among the subjects who received primary transplants, 33% are female and 74% are white. Among the subjects who had repeat transplant, 30% are female and 73% are white. There are 3753 graft failures after the first transplant, and 295 graft failures after the second one. For the first transplant, 93% of the graft failures occurred within 5 years, while for the second transplant, 83% of the graft failures occurred within 2 years. Correspondingly, we set $t_1 = 5$ years and evaluate $\hat{\theta}(t)$ every 30 days until 2 years.

6.2 Regression Modeling and Estimation of $\theta_0(t)$

The covariates we included can be categorized as being either from the recipient side or the donor side. Recipient-related covariates include age, gender, race, blood type, BMI, calendar year of the transplant, diagnosed diseases, hospitalization information, dialysis, waiting time for a transplant, model for end-stage liver disease (MELD) score components (serum creatinine, bilirubin, and INR), and albumin. The donor-related covariates are serum creatinine, BMI, donor risk index (DRI), warm ischemia time of the organ, whether death was caused by stroke, hypertension status, and diabetes history.

For the first graft failure time T_{i1} , we fitted the following proportional hazards model, as discussed in the first stage of Sect. 2, $\lambda_{i1}(t) = \lambda_0(t) \exp\{\beta_0' Z_i\}$. Significant parameter estimates based on this model are listed in Table 5. The censoring model is then fitted using the same covariates. Using Eq. (8) provided in Sect. 2, we estimate θ_0 using $\hat{\theta}(t)$ for $t = 30, 60, \dots, 720$, i.e., every month for 2 years. To reduce the impact of potentially large and imprecise weights, we capped the weight function at 10 (which is approximately the 96th

percentile of all maximum within-subject weights). The estimated hazard ratio contrasting second versus first (ref: first) transplant, $\exp\{\hat{\theta}(t)\}$, and its corresponding 95% confidence interval is presented in Fig. 1. The black solid-dotted line is $\exp\{\hat{\theta}(t)\}$ estimated at every 30 days until 2 years; the weight is capped at 10; the dashed lines are the estimated 95% confidence interval. As indicated in Fig. 1, the estimated hazard ratio decreases slightly over time before 1 year. After that, the hazard ratio is rather consistent. There is a small bump at around year 1. The reason for this bump is discussed in Sect. 7. We report in Table 6 the final estimates, $\hat{\theta}(\tau_2)$ for $\tau_2=2$ years. The estimated hazard ratio is 1.786, with an estimated standard error of 0.107. Thus, the graft failure hazard for repeat liver transplantation is estimated to be approximately 80% higher than for primary liver transplantation ($p < 0.0001$).

6.3 Piecewise Constant Model

In light of the non-proportionality suggested by $\hat{\theta}(t)$ in Fig. 1, we next applied the approach given in Sect. 5. Follow-up time subintervals were selected to be based on clinically relevant cut points, with $s_1 = 0.25$, $s_2 = 0.5$, $s_3 = 1.0$, $s_4 = 2.0$ and, again, t being specified in years post-transplant, recall that $s_0 \equiv 0$.

In Fig. 2, we show $\exp\{\widehat{\theta}_k\}$ and the corresponding 95% confidence interval for $k = 1, \dots, 4$. Point estimates (SEs) are given by $\widehat{\theta}_1=0.789(0.078)$, $\widehat{\theta}_2=0.426(0.150)$, $\widehat{\theta}_3=0.490(0.108)$, and $\widehat{\theta}_4=0.199(0.140)$. The graft failure hazard for repeat liver transplants was significantly elevated (relative to first transplants) for the first year post-retransplant. In fact, the increased GF risk associated with repeat transplantation appears to be concentrated within the first half year after transplant, and does diminish considerably thereafter. In year 2 of post-transplant follow-up, $\widehat{\theta}_4$ was not significantly different from 0.

6.4 Additional Analysis

The proposed approach implicitly assumes that the covariate effects are equal for the first and second gap time. Formal evaluation of whether $\mathbf{Z}_j$ interacted with gap time can be accomplished by fitting the more general model of [14], $\lambda_{ij}(t)=\lambda_{0j}(t)\exp\left\{\beta_j'\mathbf{Z}_i\right\}$ for $j=1, 2$, including relevant covariate-by-gap-time product terms, then testing $H_0: \boldsymbol{\beta}_1 = \boldsymbol{\beta}_2$ element-wise. Applying such testing to the liver transplant data, covariate effects generally appeared to be equal for the first and second graft failure hazards. Specifically, of the 45 tests, none were statistically significant, meaning that we had no evidence that covariate effects are unequal for the first and second graft failure hazards.

As a comparison to the proposed method, the unweighted estimates are listed in Table 7. As shown in the table, without appropriate weighting, the estimated hazard ratio will be artificially underestimated (1.506 vs. 1.786). We could have underestimated the hazard of graft failure after the second liver transplant compared to the first one, if dependent censoring was not taken into account.

Another naive method to estimate the hazard ratio would be to simply stack all data together, from both transplants, and then fit a Cox model using an indicator of retransplant. This method would be invalid because the issues of identifiability and dependent censoring are not taken into account. The results from this naive analysis are shown in Table 8. The estimated hazard ratio is 1.586, which again appears to be biased downward.

7 Discussion

In this report, we have developed semiparametric methods for contrasting gap times through a hazard ratio. The hazard ratio is widely used and fairly well accepted by clinicians and surgeons. Due to the long-standing dominance of Cox regression in observational studies involving censored data, the hazard ratio is essentially the default metric.

The proposed estimator for θ_0 has a closed form, and is intuitive because it is essentially the observed divided by the expected. The fundamental assumption of our methods is that the hazard ratio distinguishing the gap times is constant. To assess proportionality, a time-dependent sequence of estimators, $\hat{\theta}(t)$, could be computed at various pre-specified follow-up times. Lack of proportionality would be implied by a trend over t .

We applied the proposed methods to liver transplant data obtained from the SRTR. Evaluating at 2 years, we have concluded that the hazard of graft failure after the second transplant is about 80% higher than that after the first transplant. Evaluating at every 30 days until 2 years, we observed a small bump at around 1 year. Although the bump is somewhat inconsequential, we still examined it more carefully. It turned out that one patient has a large weight (≈ 100 ; capped at 10) at that time. This patient's first graft survived for 22 days, while the second one was censored alive at 341 days. Due to this patient's particular covariate pattern (The calendar year of transplant for this patient is 2012), the probability that the censoring happens after $(22 + 341)$ days is quite small. Thus, the resulting weight is large. From this example, we could see that the estimated weight can be very large sometimes. Note that, in the particular setting we consider, capping the weights seems to be the most feasible solution, especially because there does not appear to be an obvious choice for a weight stabilizer.

Some further commentary on model (1) is in order. In particular, the contrast between the gap time hazards is assumed to be equal across covariate levels. This would be a reasonable assumption in many (but certainly not all) practical cases. Dependence of θ_0 on covariates could be addressed by subsetting the data and carrying out separate analyses, e.g., separate analyses by Hepatitis C Virus (HCV) status. Another option would be estimating θ_0 by groups defined by the linear predictor ($\hat{\beta}Z_i$, a summary measure of risk).

The proposed method involves (partly) conditioning on the first gap time, $[T_{11} < t_1]$, which is a restrictive constraint. The most obvious alternative choice for avoiding the constraint is to assume independence of the gap times within-subject, which would be blatantly incorrect in many biomedical applications and, therefore, could be considered to be a stronger (and less realistic) constraint. Another seemingly obvious choice would be to assume a frailty model. However, contrasts between gap times would then not be identifiable, since there would not

be repeated failure times within-subject (for a fixed covariate vector). In summary, the set of choices is quite limited for the data structure and research question under consideration.

With respect to the implementation of IPCW, the real-data analysis showed considerable sensitivity to the value of weights. Instability caused by unduly large values of the weight function is a well-known problem associated with IPCW. Applying a cap is a well-accepted remedy, even though the value of the cap is somewhat arbitrary. It could be argued that the need for a cap on the weight function is most apparent when the estimates lack face validity (i.e., seem implausible given the previous substantive literature, or given prior knowledge of the data at hand). Most of the discussion in the literature has been in the context of estimating a regression coefficient and, in this case, the effect of huge weights may be obscured. In our case, the need for a weight was obvious since the uncapped estimator had a huge (and implausible) jump mid-way through the follow-up period. We sought to cap the weight function at a value that had an impact on the estimator, would not introduce too much bias, and had face validity in the sense of being established independently of the analysis's conclusion, e.g., in our case, we chose a round number, with only a view to smoothing the unrealistic jump in the estimator. Alternatively, if the analyst wanted to avoid using the estimator to determine how to appropriately cap the weight function, one could look at the distribution of maximum weight across subjects. For example, since this distribution will often have a long thin right tail, setting the cap equal to the 99th or 95th percentile may be warranted.

Our conclusion in the application is, in general, consistent with what was found in the literature, i.e., the outcomes of the repeat liver transplant are inferior to those of the primary transplant. However, our study is the largest study so far, uses the most up-to-date data, and is statistically valid. In addition, we contrasted the transplants by estimating a hazard ratio, which is not available in most related studies which often rely on results that (in addition to not being properly weighted) were not covariate-adjusted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.

Analysis of SRTR data: $\exp\{\hat{\theta}(t)\}$ = estimated hazard ratio for second liver transplant (ref=first)

Fig. 2.

Analysis of SRTR data using piecewise constant hazard ratio: $\exp\{\widehat{\theta}_k\}$ = estimated hazard ratio for second liver transplant (ref=first)

Table 1

Simulation study: data configurations

Setting	λ_0^C	α_1	α_2	ρ
A	0.2	0.2	-0.2	0.3
B	0.2	0.2	-0.2	0.5
C	0.2	0.2	-0.2	0.7
D	0.3	0.2	-0.2	0.3
E	0.3	0.2	-0.2	0.5
F	0.3	0.2	-0.2	0.7

Table 2

Simulation study: results for $\hat{\theta}(t)$, based on $n = 250$

Setting	t	BIAS	ESD	ASE	ECP
A	1	-0.001	0.129	0.129	0.949
	2	-0.004	0.114	0.114	0.955
	3	-0.004	0.113	0.112	0.954
B	1	-0.002	0.117	0.118	0.960
	2	-0.001	0.107	0.106	0.952
	3	-0.002	0.108	0.107	0.955
C	1	-0.002	0.102	0.105	0.961
	2	0.001	0.097	0.097	0.955
	3	-0.001	0.102	0.102	0.959
D	1	-0.004	0.138	0.138	0.947
	2	-0.005	0.128	0.124	0.946
	3	-0.007	0.129	0.125	0.946
E	1	-0.004	0.127	0.128	0.945
	2	-0.002	0.122	0.118	0.942
	3	-0.003	0.124	0.122	0.955
F	1	-0.007	0.113	0.116	0.948
	2	0.000	0.113	0.110	0.956
	3	-0.002	0.120	0.119	0.958

Table 3
Simulation results based on 1000 replicates, $n = 125$, weight capped at 97.5th percentile of maximum subject-specific weights

Setting	t	BIAS	ESD	ASE	ECP
A	1	-0.005	0.186	0.183	0.949
	2	-0.001	0.161	0.161	0.947
	3	-0.004	0.157	0.159	0.948
B	1	-0.001	0.170	0.167	0.948
	2	0.003	0.150	0.150	0.937
	3	0.000	0.148	0.151	0.950
C	1	0.001	0.149	0.149	0.959
	2	0.004	0.134	0.137	0.954
	3	0.001	0.139	0.142	0.954
D	1	-0.007	0.200	0.196	0.949
	2	-0.001	0.176	0.176	0.949
	3	-0.003	0.173	0.175	0.951
E	1	-0.004	0.185	0.181	0.950
	2	0.002	0.168	0.165	0.942
	3	0.001	0.166	0.168	0.949
F	1	0.002	0.165	0.164	0.956
	2	0.009	0.154	0.154	0.950
	3	0.009	0.159	0.160	0.947

Table 4

Performance of naive analysis of data generated as in Table 2, with $n = 250$

Setting	BIAS	ESD	ASE	ECP
A	-0.019	0.099	0.111	0.976
B	0.007	0.094	0.111	0.989
C	0.035	0.087	0.111	0.983
D	0.015	0.112	0.120	0.972
E	0.057	0.105	0.120	0.961
F	0.101	0.096	0.120	0.928

Table 5Analysis of SRTR data: parameter estimates ($p < 0.05$) for the $\lambda_{il}(t)$ model

Covariate	$\hat{\beta}$	SE($\hat{\beta}$)	$\exp\{\hat{\beta}\}$	p
Race				
White	0	0	1	–
African American	0.332	0.051	1.393	<0.0001
Other	0.299	0.149	1.348	0.045
Hepatitis C				
Yes	0.266	0.051	1.305	<0.0001
Non-cholestatic cirrhosis				
Yes	–0.277	0.052	0.758	<0.0001
Cholestatic cirrhosis				
Yes	–0.181	0.073	0.835	0.013
Hospitalization				
No	0	0	1	–
Yes, ICU	0.160	0.061	1.174	0.009
Age at transplant	–0.018	0.002	0.982	<0.0001
Donor BMI				
[20,25)	0	0	1	–
[35,60]	–0.195	0.064	0.823	0.002
log(DRI)	1.196	0.073	3.305	<0.0001
Donor diabetes				
Yes	0.265	0.052	1.303	<0.0001
Calendar year	–0.078	0.009	0.925	<0.0001

Table 6

Analysis of SRTR data: estimate of $\exp\{\theta_0\}$ for second (vs first) liver transplants; $\tau_2 = 2$ years; Proposed estimator given in (8)

	Estimate	SE	95% CI	<i>p</i>
$\hat{\theta}(\tau_2)$	0.580	0.060	(0.463, 0.697)	<0.0001
$\exp\{\hat{\theta}(\tau_2)\}$	1.786	0.107	(1.577, 1.996)	<0.0001

Table 7

Unweighted analysis of SRTR data: estimate of $\exp\{\theta_0\}$ for second (vs first) liver transplants; $\tau_2 = 2$ years;
 Unweighted estimator, obtained by replacing $W_{I2}(t, t_1)$ in (8) with 1

	Estimate	SE	95% CI	<i>p</i>
$\hat{\theta}$	0.409	0.067	(0.279, 0.540)	<0.0001
$\exp\{\hat{\theta}\}$	1.506	0.100	(1.309, 1.703)	<0.0001

Table 8

Naive analysis of SRTR data: estimate of $\exp\{\theta_0\}$ for second (vs first) liver transplants; $\tau_2 = 2$ years; Naive estimator, obtained by through unweighted partial likelihood

Gap time	$\hat{\theta}$	$SE(\hat{\theta})$	$\exp\{\hat{\theta}\}$	p
1st (ref.)	0	0	1	–
2nd	0.461	0.067	1.586	<0.0001