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Semiparametric Contrasts of Cumulative Pre-Treatment Mortality in the Presence of Dependent Censoring

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Abstract

In clinical settings, the necessity of treatment is often measured in terms of the patient's prognosis in the absence of treatment. Along these lines, it is often of interest to compare subgroups of patients (e.g., based on underlying diagnosis) with respect to pre-treatment survival. Such comparisons may be complicated by at least two important issues. First, mortality contrasts by subgroup may differ over follow-up time, as opposed to being constant, and may follow a form that is difficult to model parametrically. Moreover, in settings where the proportional hazards assumption fails, investigators tend to be more interested in cumulative (as opposed to instantaneous) effects on mortality. Second, pre-treatment death is censored by the receipt of treatment and in settings where treatment assignment depends on time-dependent factors that also affect mortality, such censoring is likely to be informative. We propose semiparametric methods for contrasting subgroup-specific cumulative mortality in the presence of dependent censoring. The proposed estimators are based on the cumulative hazard function, with pre-treatment mortality assumed to follow a stratified Cox model. No functional form is assumed for the nature of the non-proportionality. Asymptotic properties of the proposed estimators are derived, and simulation studies show that the proposed methods are applicable to practical sample sizes. The methods are then applied to contrast pre-transplant mortality for acute versus chronic End-Stage Liver Disease patients.

Keywords

Cumulative hazard; Informative censoring; Inverse weighting; Proportional hazards regression; Survival analysis; Stratification

1 Introduction

In the study of serious chronic illnesses, whether or not a particular treatment is administered may depend on the treatment's side effects and/or simply its availability. In such settings, the necessity of treatment then becomes a consideration, and may be measured

in terms of the probability of survival in the absence of treatment. Along these lines, it is often of interest to compare subgroups of patients (e.g., based on underlying diagnosis) with respect to pre-treatment survival. The general setting of our interest arises frequently. Essentially, patient subgroups are defined by a characteristic (or combination of characteristics) known at the beginning of follow-up (e.g., at diagnosis). Chief interest lies in comparing patient subgroups with respect to survival in the absence of treatment. Contrasts in subgroup-specific mortality are not expected to be constant over time, in violation of the proportional hazards assumption. Longitudinal measurements are made on patients, and both pre-treatment death and treatment assignment rates depend on such time-dependent factors. Since the pre-treatment death model of interest only conditions on information known at baseline (i.e., time $t = 0$), the receipt of treatment informatively censors pre-treatment death.

The motivation for the proposed methods arises from the End-Stage Liver Disease (ESLD) setting. The preferred treatment for ESLD is deceased-donor liver transplantation. However, the number of available organs is always (thousands) less than the number of patients in need of a liver transplant, resulting in the need for a wait list. According to the current liver allocation rules, patients perceived to be the sickest (patients with acute liver failure; designated as “Status 1”) receive the highest priority for liver transplantation (and are therefore placed at the top of the wait list), followed by chronic liver disease patients, who are sequenced in decreasing order of Model for End-Stage Liver Disease (MELD) score. Note that MELD scores are updated over time and, thus, MELD is a time-varying covariate. MELD scores are highly predictive of both pre-transplant mortality and (due to the liver allocation rules) transplant rates. Therefore, liver transplantation represents dependent censoring for pre-transplant death unless adjustment is made for the time-dependent predictors, such as MELD score. However, adjusting for time-dependent covariates will bias the between-subgroup contrasts of interest toward the null. As a result, the receipt of a liver transplant results in the dependent censoring of pre-transplant death, in the presence of adjustment for baseline (time 0) covariates only. Preliminary analysis has revealed that the Kaplan–Meier curve for high-MELD patients later crosses that for Status 1 patients, which implies that the pre-transplant death hazards for Status 1 and high-MELD patients are not proportional. Another issue is that a patient may be permanently removed or made temporarily inactive on the wait list, usually due to declining health condition; during which time intervals, the patient is ineligible to receive a liver transplant.

In the context of the Cox [6] model, non-proportionality could be handled by assuming that the subgroup-specific hazard ratios change according to a specific pattern over time that can be represented parametrically. For example, the effect could be piece-wise constant, or could follow some other continuous function. However, it is generally quite challenging to confirm the correctness of the selected parametric form. More importantly, when the effect is time varying, investigators tend to be more interested in the cumulative effect; i.e. if and when the subgroup-specific survival (or, equivalently the cumulative hazard) functions cross. Several methods have recently been proposed to estimate cumulative effects; e.g., Wei and Schaubel [21]; Tang and Wahed [20]; Boyd et al. [3]; Dong and Matthews [9]. Note that simply ignoring a time-varying effect leads to a parameter which is essentially constructed through a weighted average over time, which is poorly defined and generally

dependent on the censoring distribution. Methods for producing an appropriately averaged hazard ratio have been developed by Kalbfleisch and Prentice [13] and Xu and O'Quigley [22].

Each of the existing methods cited in the preceding paragraph makes the traditional independent censoring assumption. As previously described, dependent censoring would arise frequently in the data structure of our interest, since the death and censoring processes depend on overlapping time-varying covariates. Effect estimators that rely on censoring and death being independent are generally no longer consistent in the presence of dependent censoring. If adjustment is made for the covariates that vary over time, the effect estimate then represents a difference between subjects with equal covariate paths over time, which is usually of secondary interest at most. Robins and Rotnitzky [16] proposed Inverse Probability of Censoring Weighting (IPCW) to obtain consistent estimators in the presence of dependent censoring. In Sect. 6, we contrast the proposed methods with many existing methods which accommodate dependent censoring through IPCW, such as Robins et al. [17]; Hernan et al. [10,11]; Chen and Tsiatis [5]; Schaubel and Wei [18]; and Zhang and Schaubel [23].

In this article, we propose the ratio of IPCW-weighted integrated hazards as an estimator of the cumulative subgroup effect on mortality. The proposed methods employ a stratified Cox model with the subgroups to be compared serving as strata. The methods require no assumptions on the pattern of the subgroup effect on mortality over time, although proportionality is assumed to hold within-subgroup for the adjustment covariates. The ratio of stratum-specific cumulative hazards is used to estimate the cumulative treatment effect over time. Essentially, the proposed method extends that of Wei and Schaubel [21] to the dependent censoring setting. For the data analysis which motivated the proposed methods, patients may have periods (temporary or permanent) of treatment ineligibility; as such the methods explicitly account for treatment-ineligible time subintervals.

The remainder of this article is organized as follows. In Sect. 2, we provide the notation and describe the proposed estimator. Asymptotic properties of the proposed estimator are given in Sect. 3. Simulation studies are provided in Sect. 4 to evaluate the performance of the methods in finite samples. The proposed methods are applied to liver pre-transplant mortality using data from a national registry in Sect. 5. In Sect. 6, we provide some discussion and concluding remarks. Proofs of the asymptotic results are given in the Web Appendix.

2 Proposed Methods

First, we set up the necessary notation. Let D_i represent time until pre-treatment death for subject i , with $i = 1, \dots, n$. We assume that D_i may be right censored at treatment time, T_i , or independent censoring time, C_i , and therefore we only observe $X_i = (D_i \wedge T_i \wedge C_i)$ where $a \wedge b = \min(a, b)$. We denote the death counting process by $N_i(t) = I(D_i \leq t, D_i < C_i \wedge T_i)$, with associated increment $dN_i(t) = N_i(t^- + dt) - N_i(t^-)$ and at-risk process, $Y_i(t) = I(X_i \geq t)$, where $I(B) = 1$ if condition B is true and 0 otherwise. We define the counting process for treatment as $N_i^T(t) = I(T_i \leq t, T_i < D_i \wedge C_i)$. Let $A_i(t)$ be 1 if patient i is eligible to receive treatment at

time t , and 0 otherwise. Since treatment is never assigned while a patient is treatment ineligible, we have $dN_i^T(t) = A_i(t)dN_i^T(t)$. Let G_i denote the subgroup to which subject i belongs, with G_i being known at time $t = 0$. Let J be the number of subgroups to be compared, such that $G_i = 0, \dots, J - 1$. The variate through which “subgroup” is defined is the factor of chief interest, with the first subgroup ($j = 0$) serving as the reference category. We define $G_{ij} = I(G_i = j)$, as well as $Y_{ij}(t) = Y_i(t)G_{ij}$, $N_{ij}(t) = N_i(t)G_{ij}$ and $N_{ij}^T(t) = N_i^T(t)G_{ij}$. The covariate vector is given by $\mathbf{Z}_i(t)$, and we set $\mathbf{Z}_{i0} \equiv \mathbf{Z}_i(0)$. The covariate and treatment-eligibility histories for subject i up to time t are given by $\mathbf{Z}_i(t) = \{\mathbf{Z}_i(s); s \in [0, t)\}$ and $\tilde{A}_i(t) = \{A_i(s); s \in [0, t)\}$, respectively.

A variant of Inverse Probability of Censoring Weighting (IPCW) is used to overcome the dependent censoring of D_i via T_i . First, we assume that the cause-specific hazard for treatment

$$\lambda_i^T(t) = \lim_{\delta \rightarrow 0} \frac{1}{\delta} P(t \leq T_i \wedge D_i < t + \delta, T_i < D_i | T_i \wedge D_i > t, G_i, \tilde{\mathbf{Z}}_i(t), \tilde{A}_i(t))$$

follows the following proportional hazards model,

$$\lambda_{ij}^T(t) = A_i(t)\lambda_{0j}^T(t)\exp\{\boldsymbol{\theta}'_0 \mathbf{Z}_i^\dagger(t)\}, \quad (1)$$

wherein the subgroup effect is represented non-parametrically by the baseline hazard. The covariate $\mathbf{Z}_i^\dagger(t)$ is assumed to capture the information in $\{\mathbf{Z}_i(t), \tilde{A}_i(t)\}$ pertinent to the treatment hazard. As described by Robins and Rotnitzky [16] and Robins and Finkelstein [15], the appropriate weight to recover the absence-of-treatment scenario is then given by $W_{ij}(t) = Y_{ij}(t)\exp\{A_{ij}^T(t)\}$, where $A_{ij}^T(t) = \int_0^t A_i(s)\exp\{\boldsymbol{\theta}'_0 \mathbf{Z}_i^\dagger(s)\}\lambda_{0j}^T(s)ds$. Note that the inclusion of $A_i(t)$ in (1) reflects the fact that the treatment hazard is 0 at times during which the subject is treatment ineligible; i.e., becoming inactive prevents (as opposed to censors) treatment assignment. With respect to mortality, being inactive is not being assumed to be independent of pre-treatment death. Patients are not censored when they become inactive. Becoming inactive reduces the hazard of censoring by treatment receipt, but this is accounted for by the IPCW weight.

The coefficient $\boldsymbol{\theta}_0$ is estimated by $\hat{\boldsymbol{\theta}}$, obtained through standard partial likelihood [7], as the root of the score function,

$$U^T(\boldsymbol{\theta}) = \sum_{i=1}^n \sum_{j=0}^{J-1} \int_0^\tau \left\{ \mathbf{Z}_i^\dagger(t) - \bar{\mathbf{Z}}_j^\dagger(t; \boldsymbol{\theta}) \right\} dN_{ij}^T(t),$$

where $\bar{\mathbf{Z}}_j^\dagger(t; \boldsymbol{\theta}) = \mathbf{R}_{T_j}^{(1)}(t; \boldsymbol{\theta}) / \mathbf{R}_{T_j}^{(0)}(t; \boldsymbol{\theta})$, with $\mathbf{R}_{T_j}^{(d)}(t, \boldsymbol{\theta}) = n^{-1} \sum_{i=1}^n Y_{ij}(t) \mathbf{Z}_i^\dagger(t)^{\otimes d} \exp\{\boldsymbol{\theta}' \mathbf{Z}_i^\dagger(t)\}$, $d = 0, 1, 2$, $\mathbf{z}^{\otimes 0} = 1$, $\mathbf{z}^{\otimes 1} = \mathbf{z}$ and $\mathbf{z}^{\otimes 2} = \mathbf{z}\mathbf{z}'$. The constant τ satisfies $P(X_i \leq \tau) > 0$ and will typically be set to $\max\{X_1, \dots, X_n\}$. A Breslow [4]-type estimator is given by $\hat{\Lambda}_{0j}^T(t; \hat{\boldsymbol{\theta}})$, with $\hat{\Lambda}_{0j}^T(t; \boldsymbol{\theta}) = n^{-1} \sum_{i=1}^n \int_0^t dN_{ij}^T(s) / \mathbf{R}_{T_j}^{(0)}(s, \boldsymbol{\theta})$, such that the weight function can be estimated by $\hat{W}_{ij}(t) = Y_{ij}(t) \exp\{\hat{\Lambda}_{ij}^T(t)\}$ where

$$\hat{\Lambda}_{ij}^T(t) = \int_0^t A_i(s) \exp\{\hat{\boldsymbol{\theta}}' \mathbf{Z}_i^\dagger(s)\} d\hat{\Lambda}_{0j}^T(s; \hat{\boldsymbol{\theta}}).$$

We assume that the pre-treatment death time, D_i , follows a stratified proportional hazards model, with hazard function

$$\lambda_{ij}(t) \equiv \lambda(t|G_i=j, \mathbf{Z}_{i0}) = \lambda_{0j}(t) \exp\{\boldsymbol{\beta}_0' \mathbf{Z}_{i0}\},$$

where $\mathbf{Z}_{i0} = \mathbf{Z}_i(0)$ and $\lambda_{0j}(t)$ are the unspecified baseline hazard function for subgroup j . That is, proportional hazards are not assumed across groups, but are assumed for the baseline adjustment covariate, $\mathbf{Z}_{i0}$. The regression parameter, $\boldsymbol{\beta}_0$, can be estimated as the solution to $U(\boldsymbol{\beta}, \hat{W}) = \mathbf{0}$, where the stratified inverse-weighted score function is given by

$$U(\boldsymbol{\beta}, W) = \sum_{i=1}^n \sum_{j=0}^{J-1} \int_0^\tau \{\mathbf{Z}_{i0} - \bar{\mathbf{Z}}_j(t; \boldsymbol{\beta}, W)\} W_{ij}(t) dN_{ij}(t), \quad (2)$$

with $\bar{\mathbf{Z}}_j(t; \boldsymbol{\beta}, W) = \mathbf{R}_j^{(1)}(t; \boldsymbol{\beta}, W) / \mathbf{R}_j^{(0)}(t; \boldsymbol{\beta}, W)$ and

$\mathbf{R}_j^{(d)}(t; \boldsymbol{\beta}, W) = n^{-1} \sum_{i=1}^n W_{ij}(t) \mathbf{Z}_{i0}^{\otimes d} \exp(\boldsymbol{\beta}' \mathbf{Z}_{i0})$ for $d = 0, 1, 2$. With some algebra, $dN_{ij}(t)$ in (1) can be replaced by $dM_{ij}(t) = dN_{ij}(t) - Y_{ij}(t)d\Lambda_{ij}(t)$, such that the score function can be re-written as

$$U(\boldsymbol{\beta}, W) = \sum_{i=1}^n \sum_{j=0}^{J-1} \int_0^\tau \{\mathbf{Z}_{i0} - \bar{\mathbf{Z}}_j(t; \boldsymbol{\beta}, W)\} W_{ij}(t) dM_{ij}(t).$$

A consistent estimator of $\boldsymbol{\beta}_0$ should then satisfy $E[W_{ij}(t)dM_{ij}(t)|\mathbf{Z}_{i0}] = 0$. We can write $dM_{ij}(t) = I(T_i > t)I(C_i > t)dM_{ij}^*(t)$, where $dM_{ij}^*(t) = I(D_i \geq t)[dN_{ij}^*(t) - d\Lambda_{ij}(t)]$ and $N_{ij}^*(t) = I(D_i \leq t)G_{ij}$. Under the assumed model, $E[dM_{ij}^*(t)|\mathbf{Z}_{i0}, G_i] = 0$, which leads to $E[I(T_i > t)dM_{ij}^*(t)|\mathbf{Z}_{i0}, G_i] = 0$ in the case of independent censoring. In the presence of dependent censoring, without the IPCW term $W_{ij}(t)$, $E[dM_{ij}(t)|\mathbf{Z}_{i0}, G_i] \neq 0$ since $E[dM_{ij}(t)|\mathbf{Z}_{i0}, G_i] \neq E[I(T_i > t)I(C_i > t)|\mathbf{Z}_{i0}, G_i] E[dM_{ij}^*(t)|\mathbf{Z}_{i0}, G_i]$. However, it can be

shown that $E[W_{ij}(t)dM_{ij}(t)|\mathbf{Z}_{i0}, G_i, \tilde{\mathbf{Z}}_i(t), \tilde{A}_i(t)] = 0$, and after iterating the expectation, we have $E[W_{ij}(t)dM_{ij}(t)|\mathbf{Z}_{i0}, G_i] = 0$, such that the weighted score function, (2), is unbiased. A weighted Breslow [4] estimator can then be computed as

$$\hat{\Lambda}_{0j}(t; \boldsymbol{\beta}) = n^{-1} \sum_{i=1}^n \int_0^t \frac{\hat{W}_{ij}(s) dN_{ij}(s)}{R_j^{(0)}(s; \boldsymbol{\beta}, W)},$$

and is a consistent estimator of $\Lambda_{0j}(t)$ in the presence of dependent censoring.

In practice, some values of $\hat{W}_{ij}(t)$ can be unduly large, which can result in $\hat{\boldsymbol{\beta}}$ and $\hat{\Lambda}_{0j}(t)$ being quite imprecise. In order to improve the precision of the estimate, a stabilized weight is defined as

$$W_{ij}^S(t) = Y_{ij}(t) \frac{\exp\{\Lambda_{ij}^T(t)\}}{\exp\{\Lambda_{ij}^t(t)\}},$$

where $\Lambda_{ij}^t(t)$ is the cumulative hazard from a treatment hazards model, which accounts for baseline covariate values only, $\lambda_{ij}^t(t) = \lambda_{0j}^t(t) = \exp\{\boldsymbol{\theta}'_1 \mathbf{Z}_{i0}\}$. The stabilization used here is analogous to that of several previous authors; e.g., Robins and Finkelstein [15], Miloslavsky et al. [14], Zhang and Schaubel [23]. Hereafter, we refer to $W_{ij}(t)$ as the “unstabilized” weight.

To compare each subgroup to the reference subgroup with respect to cumulative pre-treatment mortality, the following measure is proposed,

$$\phi_j(t) = \frac{\Lambda_{ij}(t|\mathbf{Z}_{i0}=z)}{\Lambda_{i0}(t|\mathbf{Z}_{i0}=z)} = \frac{\Lambda_{0j}(t)}{\Lambda_{00}(t)},$$

for $j = 1, 1, \dots, J-1$. Substituting the previously listed cumulative hazard estimators into $\phi_j(t)$ implies the estimator,

$$\hat{\phi}_j(t) = \frac{\hat{\Lambda}_{0j}(t, \hat{\boldsymbol{\beta}})}{\hat{\Lambda}_{00}(t, \hat{\boldsymbol{\beta}})} \quad t \in [t_L, t_U],$$

where t_L is chosen to be large enough to avoid $\hat{\Lambda}_{00}(t, \hat{\boldsymbol{\beta}}) = 0$ and t_U is chosen to avoid instability at the tail of the observation time distribution. The measure $\phi_j(t)$ contrasts hypothetical patients who have the same covariate pattern but are in different subgroups. Note that if proportionality holds across subgroups, then $\phi_j(t)$ reduces to the time-invariant constant commonly referred to as the hazard ratio.

3 Asymptotic Properties

The asymptotic properties of the proposed methods are summarized by the following theorem.

Theorem 1

Under conditions (a) to (g) specified in the Supplementary Materials, $n^{1/2}\{\hat{\varphi}_j(t) - \varphi_j(t)\}$ converges asymptotically to a zero-mean Gaussian process with (covariance function $\sigma_j(s, t) = E[\xi_{ij}(s)\xi_{ij}(t)]$, where $\{\xi_{1j}(t), \dots, \xi_{nj}(t)\}$ are independent and identically distributed with mean 0, with

$$\xi_{ij}(t) = \frac{1}{\Lambda_{00}(t)} \Phi_{ij}(t) - \frac{\Lambda_{0j}(t)}{\Lambda_{00}^2(t)} \Phi_{i0}(t),$$

where we define

$$\begin{aligned} \Phi_{ij}(t) &= \mathbf{h}'_j(t; \beta_0, W) \boldsymbol{\Omega}^{-1}(\beta_0) \mathbf{U}_i(\beta_0) \\ &+ [\mathbf{B}'_j(t; \beta_0) + \mathbf{E}'_j(t; \beta_0)] \boldsymbol{\Omega}_T(\theta_0)^{-1} \sum_{k=0}^{J-1} \mathbf{U}_{ik}^T(\theta_0) \\ &+ \int_0^t \frac{[K_j(s, t) + P_j(s, t)]}{r_{Tj}^{(0)}(s; \theta_0)} dM_{ij}^T(s) \\ &+ \int_0^t r_j^{(0)}(u; \beta_0, W)^{-1} W_{ij}(u) dM_{ij}(u), \end{aligned}$$

where $\mathbf{r}_j^{(p)}(t; \beta, W) = E[W_{ij}(t) \mathbf{Z}_{i0}^{\otimes p} \exp(\beta' \mathbf{Z}_{i0})]$ is the limiting value of $\mathbf{R}_j^{(p)}(t; \beta, W)$ defined earlier (for $p = 0, 1, 2$),

$$\bar{\mathbf{z}}_j(t; \beta, W) = \mathbf{r}_j^{(1)}(t; \beta, W) / r_j^{(0)}(t; \beta, W), \mathbf{h}_j(t; \beta, W) = - \int_0^t \bar{\mathbf{z}}_j(u; \beta, W) d\Lambda_{0j}(u),$$

$$\begin{aligned} \boldsymbol{\Omega}(\beta) &= E \left[\sum_{j=0}^{J-1} \int_0^\tau \left\{ \frac{\mathbf{r}_j^{(2)}(t; \beta, W)}{r_j^{(0)}(t; \beta, W)} - \bar{\mathbf{z}}_j(t; \beta, W)^{\otimes 2} \right\} W_{ij}(t) dN_{ij}(t) \right] \\ \mathbf{U}_i(\beta) &= \sum_{j=0}^{J-1} \int_0^\tau \{ \mathbf{Z}_{i0} - \bar{\mathbf{z}}_j(t; \beta, W) \} W_{ij}(t) dM_{ij}(t) + \mathbf{H}'(t; \beta, W) \boldsymbol{\Omega}_T(\theta)^{-1} \sum_{j=0}^{J-1} \mathbf{U}_{ij}^T(\theta) + \sum_{j=0}^{J-1} \int_0^\tau \mathbf{T}(u) r_{Tj}^{(0)}(u; \theta_0)^{-1} dM_{ij}^T(u) \\ \mathbf{H}(t; \beta, W) &= E \left[\sum_{j=0}^{J-1} \int_0^\tau \{ \mathbf{Z}_{i0} - \bar{\mathbf{z}}_j(t; \beta, W) \} W_{ij}(t) \mathbf{D}_{ij}(t; \theta_0) dM_{ij}(t) \right] \\ \mathbf{D}_{ij}(t; \theta) &= \int_0^t \left\{ \mathbf{Z}_i(u) - \bar{\mathbf{z}}_j^\dagger(u; \theta) \right\}' d\Lambda_{ij}^T(u) \\ \mathbf{U}_{ij}^T(\theta) &= \int_0^\tau \left\{ \mathbf{Z}_i(t) - \bar{\mathbf{z}}_j^\dagger(t; \theta) \right\} dM_{ij}^T(t; \theta) \\ \mathbf{T}(u) &= E \left[\sum_{j=0}^{J-1} \int_0^\tau e^{\theta_0' \mathbf{Z}_i(u)} \int_u^\tau \{ \mathbf{Z}_{i0} - \bar{\mathbf{z}}_j(t; \beta, W) \} W_{ij}(t) dM_{ij}(t) \right], \end{aligned}$$

with $dM_{ij}(t) = dN_{ij}(t) - Y_{ij}(t) d\Lambda_i^T(t)$ and $dM_{ij}^T(t) = dN_{ij}^T(t) - Y_{ij}(t) d\Lambda_i^T(t)$.

The quantities $B_j(t; \beta)$, $P_j(u, t)$, $F_j(u)$, and $Q_j(s, u)$ are defined in the Supplementary Materials.

Consistency can be demonstrated by combining fundamental results from Robins and Rotnitzky [16], Robins and Finkelstein [15]; see also Zhang and Schaubel [23]; basic Martingale theory (e.g., Andersen and Gill [1]; Fleming and Harrington [8]); as well as various results from empirical process theory (e.g., Biliak et al. [2]; Lin et al. [12]). Asymptotic normality can be demonstrated by deriving (through Taylor series expansions) then combining the influence functions for various expressions. A proof of Theorem 1 is given in the Supplementary Materials. The asymptotic variance can be estimated consistently by $\hat{\sigma}_j^2(t) = n^{-1} \sum_{i=1}^n \hat{\xi}_{ij}(t)^2$, where $\hat{\xi}_i(t)$ is obtained by replacing all limiting values in ϕ_i by their empirical counterparts.

The proof of theorem 1 pertains to the unstabilized weight, $W_{ij}(t)$, while a stabilized version, $W_{ij}^S(t)$, would usually be preferred. The computation of the variance is quite complicated (as implied by Theorem 1) and is further complicated by the stabilizer, which is also an estimated quantity. A computationally simpler variance treats the weight, be it $\hat{W}_{ij}(t)$ or $\hat{W}_{ij}^S(t)$, as fixed, in which case the variance estimator simplifies to $\tilde{\sigma}_j^2(t) = n^{-1} \sum_{i=1}^n \tilde{\xi}_{ij}(t)^2$, where

$$\begin{aligned}\tilde{\xi}_{ij}(t) &= \frac{1}{\hat{\lambda}_{00}(t)} \tilde{\Phi}_{ij}(t) - \frac{\hat{\lambda}_{0j}(t)}{\hat{\lambda}_{00}^2(t)} \tilde{\Phi}_{i0}(t), \\ \tilde{\Phi}_{ij}(t) &= \hat{h}_j'(t) \hat{\Omega}^{-1}(\hat{\beta}) \tilde{U}_i(\hat{\beta}) + \int_0^t R_j^{(0)}(u; \hat{\beta}, \hat{W})^{-1} \hat{W}_{ij}(u) d\hat{M}_{ij}(u) \\ \tilde{U}_i(\beta) &= \sum_{j=0}^{J-1} \int_0^\tau \{Z_{i0} - \bar{Z}_j(t; \beta, W)\} \hat{W}_{ij}(t) d\hat{M}_{ij}(t).\end{aligned}\quad (3)$$

In the interests of computational convenience, we recommend the simplified variance estimator and, as such, evaluate this version through simulations described in the next section.

4 Simulation Studies

For each simulated subject ($i = 1, \dots, n$), a baseline covariate, Z_{i0} , was first created as a standard normal variate truncated at -4 and 4 . The group indicator ($G_i = 0, 1$) was then generated from a Bernoulli distribution with parameter $\exp(-0.6Z_{i0}) / \{1 + \exp(-0.6Z_{i0})\}$. The death time, D_i , was then generated by transforming $\varepsilon_{1i} \sim \text{Uniform}(0, 1)$ using the inverse of the cumulative distribution function of a Weibull distribution with hazard function

$$\lambda_{ij}(t) = \alpha_j \gamma_j t^{\gamma_j - 1} \exp\{\beta_0 Z_{i0}\}. \quad (4)$$

Two subgroups were compared, $j = 0, 1$, with each subgroup consisting of an equal number of subjects.

Unless $\gamma_0 = \gamma_1$, subgroup-specific hazards would not be proportional. Various values of γ_0 and γ_1 were chosen, in order to produce a constant, increasing or decreasing cumulative hazard ratio, $\varphi_1(t) = \Lambda_{01}(t)/\Lambda_{00}(t)$. We generated a time-dependent covariate which correlated with both death time D_i and treatment time T_i conditional on (G_i, Z_{i0}) . First, let $V_{ti} = -2 \log\{G_i \varepsilon_{1i} + (1 - G_i)(1 - \varepsilon_{1i})\} + \varepsilon_{2i}$, where $\varepsilon_{2i} \sim \text{Uniform}(0,1)$, and define $V_i(t) = I(V_{ti} \leq t)$. Thus, $V_i(t)$ is correlated with D_i even conditional on (G_i, Z_{i0}) . Treatment time was generated to follow the proportional hazards model,

$$\lambda_i^T(t) = \lambda_0^T(t) \exp\{\theta_0 + \theta_G G_i + \theta_Z Z_{i0} + \theta_1 V_i(t)\}, \quad (5)$$

such that $V_i(t)$ correlates with T_i . Consequently, D_i is dependently censored by T_i , even conditional on (G_i, Z_{i0}) . To simplify the setup, administrative censoring time C_i is not involved in the simulation study. Data pertaining to death time $\{X_i, N_i(X_i), \mathbf{Z}_i\}$ is used to fit model (4), with time to treatment data $\{X_i, N_i^T(X_i), \mathbf{Z}_i, V_i(X_i)\}$ used to fit model (5).

We present results for samples of size $n = 500$ and 250 and censoring (via treatment) percentages of 10, 30, and 50 %. The censoring percentage was varied by changing θ_0 . The parameters $[\beta_0, \alpha_0, \alpha_1, \theta_G, \theta_Z, \theta_1]$ are set to $[0.3, 0.2, 0.4, 0.2, 0.2, 0.3]$. The vector $[\gamma_0, \gamma_1]$ was set to each of $[1.5, 1.5]$, $[1.5, 1.25]$ and $[1, 1.5]$, to make $\varphi_1(t) = \Lambda_{01}(t)/\Lambda_{00}(t)$ a constant, an increasing function and a decreasing function, respectively. The properties of $\varphi_1(t)$ were studied at times $t = 1, 2$, and 3 . Both the unstabilized weight, $W_{ij}(t)$, and stabilized weight, $W_{ij}^S(t)$, were applied to the simulated data, as was the weight function $W_{ij}(t) = 1$ which is valid only when censoring is independent. We used the simplified variance estimator given in (3), which treats the IPCW weights as fixed. A total of 500 replicates were generated per data configuration.

Tables 1, 2, and 3 show the results when $\varphi_1(t)$ is increasing, decreasing, and constant, respectively. All estimates are approximately unbiased. The magnitude of the finite-sample bias generally increases as the sample size decreases. There is no obvious association between the degree of bias and treatment percentage. On the one hand, one might expect that higher treatment percentages should increase bias since the dependent censoring aspect figures more prominently in the death model's estimating function. On the other hand, a greater number of observed treatment times should generally result in modeling $\Lambda_i^T(t)$ more precisely, and hence, diminish the bias. Generally, the average asymptotic standard error (ASE) is close to the empirical standard error (ESE). Coverage probability (CP) tended to decrease as the sample size decreased.

Note that simulation results were not very good for the $n = 100$ case (data not shown). The proposed method would generally not be recommended for smaller samples sizes (i.e., <100 subjects per group), except perhaps in settings where the dependent censoring rate was low.

5 Analysis of Liver Data

We applied the proposed methods in order to compare acute liver failure patients (classified as Status 1) and chronic ESLD patients (classified by MELD score) with respect to pre-

transplant mortality. The study population consisted of patients initially placed on the wait list for deceased-donor liver transplantation between March 1, 2002 and December 31, 2009 in United States. Data were obtained from the Scientific Registry of Transplant Recipients (SRTR). Only patients age ≥ 18 at listing were included in our study sample, and we excluded re-transplant candidates.

In order to construct the IPCW weight, the following time-dependent stratified Cox model was fitted,

$$\lambda_{ir}^T(t) = A_i(t) \lambda_{0r}^T(t) \exp\{\boldsymbol{\theta}_0' \mathbf{Z}_i^\dagger(t)\},$$

where the subscript $r = 1, \dots, 11$ stands for United Network for Organ Sharing (UNOS) Region. The indicator $A_i(t) = 1$ if the patient is active on the wait list and 0 otherwise; i.e., patients do not contribute to the estimation of $\boldsymbol{\theta}_0$ or $\lambda_{0r}^T(t)$ while they are removed from or inactive on the wait list. The covariate $\mathbf{Z}_i^\dagger(t)$ included current MELD score, Status 1, albumin, age, gender, race, diagnosis of Hepatitis C, body mass index, diabetes, hospitalization, blood type, dialysis within prior week, encephalopathy, ascites, and serum creatinine. We used two types of weights, $W_{ij}(t)$ and $W_{ij}^S(t)$. Even for the stabilized weight, some extreme values existed. Since 99 % of the estimated weights were less than 10, the weights were then capped at 10. For comparison purposes, we also evaluated the unweighted estimator, $W_{ij}(t) = 1$, developed by Wei and Schaubel [21].

The model of main interest (that for the pre-transplant death hazard) is given by

$$\lambda_{ij}(t) = \lambda_{0j}(t) \exp\{\boldsymbol{\beta}_0' \mathbf{Z}_{i0}\},$$

with the subscript j corresponding to Status 1 ($j = 0$; reference) and $j = 1, \dots, 7$ corresponding MELD score category (21–23, 24–26, 27–29, 30–32, 33–35, 36–40, >40, respectively). The baseline covariate vector, $\mathbf{Z}_{i0}$, included the following terms (each recorded at the time of wait list): albumin, age, gender, race, diagnosis, body mass index, diabetes, hospitalization, dialysis within prior week, and previous malignancy. Although the MELD score is capped at 40 for allocation purposes, in our analysis, calculated MELD scores over 40 were collected into a >40 group.

A total of 66,884 subjects were eligible for our study. We focused on comparing the MELD >20 categories (chronic ESLD patients) to Status 1 (acute liver failure patients). Restricting attention to Status 1 and MELD > 20, the sample size was $n = 16,684$. The cumulative hazard ratio for each high-MELD category, relative to Status 1, could be estimated reliably out to 5 years post-wait list. Since results with $W_{ij}(t)$ are similar to those with $W_{ij}^S(t)$, we only show results based on the stabilized weight.

Estimated cumulative hazard ratios are shown in Fig. 1 (for MELD >40, 33–35, 27–29, and 21–23, each relative to Status 1) and Fig. 2 (for MELD 36–40, 30–32, and 24–26). Point

estimates and point-wise 95 % confidence intervals are shown in Fig. 3 (for MELD >40), Fig. 4 (MELD 36–40), and Fig. 5 (MELD 21–23). In each case, the cumulative hazard ratio for the MELD groups eventually becomes significantly greater than 1. For example, even for the lowest MELD group, we considered, MELD 21–23, the cumulative hazard ratio crosses 1 at approximately 9 months after wait list and attains statistical significance at approximately the 1 year point.

For the MELD 36–40 group, the weighted and unweighted [21] estimators are compared in Fig. 6. It can be seen that the cumulative hazard ratio is underestimated by approximately 0.5 by failure to account for dependent censoring via liver transplantation.

It is interesting that Status 1 patients apparently have lower mortality compared to any of the high-MELD categories we examined. In practice, acute patients automatically lose their Status 1 designation after 14 days, since they are very likely to die within 2 weeks. In fact, patients must apply to have their Status 1 classification re-certified after 7 days. It is assumed that if they were ill enough to warrant Status 1 designation, they would die within one week in the absence of a liver transplant. However, it appears that a large portion of patients who were Status 1 at baseline live for several years after wait list.

6 Discussion

In this article, we use the ratio of the subgroup-specific integrated hazard functions as a time-dependent measure of the covariate-adjusted cumulative effect of subgroup on mortality. Under the target data structure, covariates are time varying. The death hazard model of interest adjusts for only time 0 covariates, such that pre-treatment death may be dependently censored due to mutual correlation between the values of the time-varying covariates (after time 0) with both the death and censoring (i.e., treatment) times. Inverse weighting (IPCW) is used to obtain unbiased estimators, with a stabilized weight suggested. The fact that subjects may experience time intervals of treatment ineligibility is handled by fitting a treatment hazard model that is conditional on being eligible, with subjects' ineligible periods then zeroed out in the probability-of-remaining-untreated calculation. Simulations show that the proposed methods work well in reasonable sized samples. Finally, the proposed methods are used to contrast pre-transplant mortality between acute and chronic liver failure patients.

The intention of the Status 1 designation is to distinguish patients who will die very soon if they do not receive a liver transplant. Very few comparisons between the mortality of Status 1 and high-MELD patients have been carried out, primarily since it is generally assumed by the liver transplant community that mortality is much higher for acute relative to chronic liver failure patients. However, based on a conventional time-dependent model and capping follow-up at 14 days, Sharma et al. [19] reported that wait list mortality for high-MELD patients was very comparable to that of Status 1 patients. Moreover, Sharma et al. [19] found that MELD > 40 was associated with significantly higher 2-week mortality than Status 1. Results from our current analysis in Sect. 5 provide further evidence that the prioritization for deceased-donor liver transplantation of Status 1 over MELD > 40 patients

needs to be reconsidered. Even patients with MELD 21–23 at listing had significantly greater cumulative pre-transplant mortality than Status 1 patients.

Various methods related to those proposed in this article can be found in the existing literature, although none estimate the quantity of interest under the assumed data structure. In particular, Robins et al. [17] and Hernan et al. [10,11] developed methods for estimating the average causal effect in terms of the hazard ratio. Although the methods allow for treatment to be time varying, proportional hazards are assumed under the marginal structural model employed. Chen and Tsiatis [5], Schaubel and Wei [18], and Zhang and Schaubel [23] used restricted mean survival time as an effect measure, such that subgroup contrasts are cumulative in nature. However, contrasts between restricted mean lifetime do not describe how the essential effect changes over time. Note that each of these methods estimates an average causal effect, which would be of interest in many but not all settings. In many applications (such as our motivating example), it is of greater interest to compare patient subgroups with “all else equal” for reasons of interpretation. The estimator proposed in this article is analogous to that of Wei and Schaubel [21], but allows for a richer covariate structure and more general censoring patterns. In summary, due to interest in the shape of the time-varying effect, the presence of dependent censoring and the potential for subjects to become treatment ineligible, none of the aforementioned methods can be applied to our ESLD motivating example directly.

The motivating example specifically focused on pre-treatment survival. It would be of interest to extend the proposed methods to estimate treatment effects.

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References

1. Andersen PK, Gill RD. Cox's regression model for counting processes: a large sample study. *Ann Stat.* 1982; 10:1100–1120.
2. Biliak Y, Gu M, Ying Z. Towards a general asymptotic theory for the Cox model with staggered entry. *Ann Stat.* 1997; 25:662–682.
3. Boyd AP, Kittelson JM, Gillen DL. Estimation of treatment effect under non-proportional hazards and conditionally independent censoring. *Stat Med.* 2012; 31:3504–3515. [PubMed: 22763957]
4. Breslow NE. Discussion of the paper by D. R. Cox. *J R Stat Soc B.* 1972; 34:216–217.
5. Chen P, Tsiatis AA. Causal inference on the difference of the restricted mean lifetime between two groups. *Biometrics.* 2001; 57:1030–1038. [PubMed: 11764241]
6. Cox DR. Regression models and life-tables (with discussion). *J R Stat Soc B.* 1972; 34:187–220.
7. Cox DR. Partial likelihood. *Biometrika.* 1975; 62:269–276.
8. Fleming, TR.; Harrington, DP. *Counting process and survival analysis.* Wiley; New York: 1991.
9. Dong B, Matthews DE. Empirical likelihood for cumulative hazard ratio estimation with covariate adjustment. *Biometrics.* 2012; 68:408–418.
10. Hernán MA, Brumback B, Robins JM. Marginal structural models to estimate the joint causal effect of nonrandomized treatments. *J Am Stat Assoc.* 2001; 96:440–448.

11. Hernán MA, Brumback B, Robins JM. Marginal structural models to estimate the causal effect on the survival of HIV-positive men. *Epidemiology*. 2000; 11:561–570. [PubMed: 10955409]
12. Lin DY, Wei LJ, Yang I, Ying Z. Semiparametric regression for the mean and rate functions of recurrent events. *J R Stat Soc B*. 2000; 62:711–730.
13. Kalbfleisch JD, Prentice RL. Estimation of the average hazard ratio. *Biometrika*. 1981; 68:105–112.
14. Miloslavsky M, Keles S, Van Der Laan MJ, Butler S. Recurrent events analysis in the presence of time-dependent covariates and dependent censoring. *J R Stat Soc B Met*. 2004; 66:239–257.
15. Robins JM, Finkelstein DM. Correcting for noncompliance and dependent censoring in an AIDS clinical trial with inverse probability of censoring weighted (IPCW) Log-rank tests. *Biometrics*. 2000; 56:779–788. [PubMed: 10985216]
16. Robins JM, Rotnitzky A. Recovery of information and adjustment for dependent censoring using surrogate markers. In: Jewell, N.; Dietz, K.; Farewell, B., editors. *AIDS epidemiology—methodological issues*. Birkhäuser; Boston: 1992. p. 297–331.
17. Robins JM, Hernán MA, Brumback B. Marginal structural models and causal inference in epidemiology. *Epidemiology*. 2000; 11:550–560. [PubMed: 10955408]
18. Schaubel DE, Wei G. Double inverse-weighted estimation of cumulative treatment effects under nonproportional hazards and dependent censoring. *Biometrics*. 2010; 67:29–38. [PubMed: 20560935]
19. Sharma P, Schaubel DE, Gong Q, Guidinger MK, Merion RM. End-stage liver disease candidates at the highest MELD scores have higher waitlist mortality than Status 1A candidates. *Hepatology*. 2012; 55:192–198. [PubMed: 21898487]
20. Tang X, Wahed AS. Cumulative hazard ratio estimation for treatment regimes in sequentially randomized clinical trials. *Stat Biosci*. 2013; 1007/s12561-013-9089-6
21. Wei G, Schaubel DE. Estimating cumulative treatment effects in the presence of nonproportional hazards. *Biometrics*. 2008; 64:724–732. [PubMed: 18162108]
22. Xu R, O’Quigley J. Estimating average regression effect under non-proportional hazards. *Biostatistics*. 2000; 1:423–439. [PubMed: 12933565]
23. Zhang M, Schaubel DE. Estimating differences in restricted mean lifetime using observational data subject to dependent censoring. *Biometrics*. 2011; 67:740–749. [PubMed: 21039400]

Fig. 1.
Analysis of SRTR data: cumulative hazard ratio of high-MELD patients compared to Status 1 patients (reference)

Fig. 2.
Analysis of SRTR data: cumulative hazard ratio of high-MELD patients compared to Status 1 patients (reference)

Fig. 3. Analysis of SRTR data: cumulative hazard ratio, $\hat{\varphi}_7(t)$, for MELD > 40 patients ($j = 7$) relative to Status 1 patients ($j = 0$: reference) with 95 % confidence interval

Fig. 4. Analysis of SRTR data: Cumulative hazard ratio, $\hat{\phi}_6(t)$, for MELD 36–40 patients ($j = 6$) relative to Status 1 patients (reference: $j = 0$), with 95 % confidence interval

Fig. 5. Analysis of SRTR data: Cumulative hazard ratio, $\hat{\phi}_1(t)$, for MELD 21–23 patients ($j = 1$) relative to Status 1 patients ($j = 0$: reference), with 95 % confidence interval

Fig. 6. Analysis of SRTR data: Weighted versus unweighted cumulative hazard ratio, $\hat{\varphi}_1(t)$, for MELD 21–23 patients ($j=1$) relative to Status 1 patients ($j=0$: reference)

Table 1

Simulation results of $\hat{\varphi}_1(t)$ when $\varphi_1(t)$ is increasing in t .

n	%C	t	$\varphi_1(t)$	$\hat{\varphi}_1(t) = 1$						$\hat{W}_{ij}^S(t)$					
				BIAS	BIAS	ASE	ESE	CP	BIAS	ASE	ESE	CP	BIAS	ASE	CP
500	10 %	1	0.50	0.006	0.008	0.095	0.096	0.94	0.007	0.094	0.096	0.93	0.007	0.094	0.93
		2	0.59	0.020	0.005	0.081	0.079	0.95	0.004	0.078	0.079	0.95	0.004	0.078	0.95
		3	0.66	0.026	0.007	0.083	0.083	0.95	0.007	0.077	0.084	0.93	0.007	0.077	0.93
	30 %	1	0.50	0.010	0.007	0.099	0.102	0.93	0.006	0.097	0.102	0.93	0.006	0.097	0.93
		2	0.59	0.016	0.002	0.089	0.088	0.95	0.002	0.082	0.088	0.93	0.002	0.082	0.93
		3	0.66	0.021	0.006	0.094	0.095	0.95	0.006	0.082	0.095	0.91	0.006	0.082	0.91
	50 %	1	0.50	0.018	0.009	0.104	0.107	0.93	0.008	0.101	0.107	0.93	0.008	0.101	0.93
		2	0.59	0.031	0.009	0.098	0.098	0.96	0.009	0.089	0.097	0.94	0.009	0.089	0.94
		3	0.66	0.038	0.007	0.108	0.108	0.95	0.007	0.093	0.107	0.92	0.007	0.093	0.92
250	10 %	1	0.50	0.015	0.017	0.137	0.141	0.94	0.017	0.136	0.141	0.94	0.017	0.136	0.94
		2	0.59	0.010	0.005	0.115	0.117	0.93	0.005	0.110	0.117	0.93	0.005	0.110	0.93
		3	0.66	0.012	0.009	0.117	0.121	0.94	0.010	0.109	0.121	0.93	0.010	0.109	0.93
	30 %	1	0.50	0.015	0.013	0.142	0.145	0.94	0.014	0.139	0.145	0.93	0.014	0.139	0.93
		2	0.59	0.026	0.010	0.126	0.131	0.94	0.011	0.117	0.131	0.93	0.011	0.117	0.93
		3	0.66	0.029	0.010	0.132	0.138	0.93	0.010	0.116	0.138	0.91	0.010	0.116	0.91
	50 %	1	0.50	0.010	0.012	0.148	0.156	0.93	0.011	0.143	0.155	0.92	0.011	0.143	0.92
		2	0.59	0.038	0.012	0.139	0.148	0.93	0.012	0.126	0.147	0.92	0.012	0.126	0.92
		3	0.66	0.054	0.011	0.152	0.165	0.92	0.012	0.132	0.162	0.89	0.012	0.132	0.89

Table 2

Simulation results of $\hat{\varphi}_1(t)$ when $\varphi_1(t)$ is decreasing in t .

n	%C	t	$\varphi(t)$	$\hat{\mathcal{W}}_{\theta}(t) = 1$			$\hat{W}_{ij}^S(t)$						
				BIAS	BIAS	ASE	BIAS	ASE	ESE	CP	BIAS	ASE	ESE
500	10 %	1	0.50	0.011	0.008	0.093	0.094	0.094	0.94	0.009	0.093	0.094	0.94
		2	0.35	0.004	0.002	0.050	0.051	0.051	0.94	0.002	0.049	0.051	0.93
		3	0.29	0.003	0.002	0.038	0.039	0.039	0.94	0.002	0.036	0.039	0.93
	30 %	1	0.50	0.009	0.002	0.096	0.099	0.099	0.94	0.003	0.094	0.099	0.94
		2	0.35	0.008	0.001	0.053	0.053	0.053	0.94	0.002	0.050	0.053	0.93
		3	0.29	0.009	0.002	0.042	0.042	0.042	0.94	0.002	0.037	0.042	0.91
	50 %	1	0.50	0.015	0.005	0.103	0.104	0.104	0.95	0.006	0.099	0.103	0.94
		2	0.35	0.019	0.004	0.060	0.063	0.063	0.95	0.005	0.055	0.061	0.93
		3	0.29	0.020	0.001	0.049	0.051	0.051	0.94	0.002	0.043	0.050	0.91
250	10 %	1	0.50	0.023	0.013	0.133	0.138	0.138	0.94	0.014	0.133	0.139	0.94
		2	0.35	0.009	0.005	0.070	0.072	0.072	0.94	0.005	0.069	0.072	0.94
		3	0.29	0.004	0.003	0.052	0.053	0.053	0.94	0.003	0.050	0.053	0.93
	30 %	1	0.50	0.020	0.008	0.137	0.136	0.136	0.95	0.009	0.135	0.137	0.94
		2	0.35	0.016	0.005	0.075	0.078	0.078	0.94	0.005	0.071	0.077	0.93
		3	0.29	0.013	0.001	0.057	0.059	0.059	0.94	0.001	0.052	0.058	0.91
	50 %	1	0.50	0.027	0.015	0.148	0.157	0.157	0.93	0.014	0.143	0.156	0.92
		2	0.35	0.022	-0.001	0.084	0.089	0.089	0.92	-0.001	0.077	0.087	0.90
		3	0.29	0.024	0.001	0.068	0.073	0.073	0.92	0.001	0.060	0.071	0.89

Table 3

Simulation results of $\hat{\varphi}_1(t)$ when $\varphi_1(t)$ is constant in t .

n	%C	t	$\varphi_1(t)$	$\hat{\varphi}_1(t) = 1$						$\hat{W}_{ij}^S(t)$					
				BIAS	BIAS	ASE	ESE	CP	BIAS	ASE	ESE	CP	BIAS	ASE	CP
500	10 %	1	0.50	0.010	0.007	0.094	0.098	0.94	0.007	0.093	0.098	0.94	0.007	0.093	0.94
		2	0.50	0.008	0.002	0.066	0.066	0.95	0.002	0.064	0.066	0.93	0.002	0.064	0.93
		3	0.50	0.006	0.007	0.062	0.065	0.93	0.006	0.058	0.065	0.92	0.006	0.058	0.92
	30 %	1	0.50	0.008	0.011	0.099	0.100	0.94	0.012	0.097	0.100	0.94	0.012	0.097	0.94
		2	0.50	0.014	0.006	0.073	0.076	0.94	0.007	0.068	0.076	0.93	0.007	0.068	0.93
		3	0.50	0.018	0.007	0.071	0.076	0.93	0.007	0.062	0.075	0.90	0.007	0.062	0.90
	50 %	1	0.50	0.022	0.012	0.109	0.109	0.95	0.012	0.105	0.109	0.94	0.012	0.105	0.94
		2	0.50	0.038	0.006	0.088	0.091	0.93	0.006	0.079	0.090	0.91	0.006	0.079	0.91
		3	0.50	0.045	0.003	0.093	0.102	0.91	0.003	0.080	0.100	0.87	0.003	0.080	0.87
250	10 %	1	0.50	0.027	0.020	0.137	0.146	0.94	0.020	0.136	0.146	0.94	0.020	0.136	0.94
		2	0.50	0.010	0.009	0.094	0.099	0.93	0.009	0.091	0.099	0.92	0.009	0.091	0.92
		3	0.50	0.014	0.005	0.084	0.091	0.93	0.005	0.081	0.091	0.92	0.005	0.081	0.92
	30 %	1	0.50	0.025	0.009	0.141	0.142	0.93	0.009	0.138	0.141	0.93	0.009	0.138	0.93
		2	0.50	0.020	0.008	0.105	0.107	0.94	0.007	0.097	0.107	0.92	0.007	0.097	0.92
		3	0.50	0.018	0.009	0.102	0.106	0.94	0.008	0.088	0.105	0.90	0.008	0.088	0.90
	50 %	1	0.50	0.022	0.015	0.156	0.160	0.92	0.014	0.150	0.158	0.92	0.014	0.150	0.92
		2	0.50	0.034	0.010	0.125	0.129	0.94	0.009	0.113	0.125	0.92	0.009	0.113	0.92
		3	0.50	0.046	0.022	0.133	0.144	0.92	0.020	0.116	0.142	0.88	0.020	0.116	0.88