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Estimating Cross Quantile Residual Ratio with Left-Truncated Semi-Competing Risks Data

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Abstract

A semi-competing risks setting often arises in biomedical studies, involving both a nonterminal event and a terminal event. Cross quantile residual ratio (Yang and Peng, 2016) offers a flexible and robust perspective to study the dependency between the nonterminal and the terminal events which can shed useful scientific insight. In this paper, we propose a new nonparametric estimator of this dependence measure with left truncated semi-competing risks data. The new estimator overcomes the limitation of the existing estimator that is resulted from demanding a strong assumption on the truncation mechanism. We establish the asymptotic properties of the proposed estimator and develop inference procedures accordingly. Simulation studies suggest good finite-sample performance of the proposed method. Our proposal is illustrated via an application to Denmark diabetes registry data.

Keywords

Estimating equation; Left truncation; Quantile residual time; Semi-competing risks

1 Introduction

Semi-competing risks data (Fine et al., 2001) frequently arise in biomedical studies involving multiple endpoints. A common scenario is that subjects are followed for both a nonterminal event (e.g. disease landmark event) and a terminal event (e.g. death), and time to the nonterminal event (T_1) can be censored by time to the terminal event (T_2) but not vice versa. Besides the usual interest in the nonterminal event or the terminal event, exploiting the inter-relationship/dependence between the nonterminal event and the terminal event is also a sensible effort and can lead to valuable practical implications.

Most of existing work tailored to study semi-competing risks dependence (Fine et al., 2001; Wang, 2003; Ghosh, 2006; Peng and Fine, 2007; Hsieh et al., 2008; Lakhal et al., 2008; Chen, 2012, among others) adopts the copula framework. That is, a copula model is assumed for the joint distribution of (T_1, T_2) at the upper wedge, with a copula parameter, fixed or time-dependent, capturing the dependence between T_1 and T_2 . Although this type of approach is intuitive and useful, it may be hard to verify its crucial copula assumption on the relation between the joint distribution of (T_1, T_2) and the marginal distributions. Also,

different copulas describe different dependence patterns between T_1 and T_2 , making the interpretation of a copula parameter rely on the selection of the copula function.

Recently, Yang and Peng (2016) proposed a new semi-competing risks dependence measure, *Cross Quantile Residual Ratio* (CQRR), that does not require distributional assumptions and is nonparametrically identifiable. Their basic idea, which has a similar flavor to the cross-ratio function (Oakes, 1989), is to compare the quantile residual time to the terminal event with the occurrence of the nonterminal event versus that without the occurrence of the nonterminal event. More specifically, CQRR is defined as

$$CQRR(\tau; t_0) = \frac{Q_\tau(T_2 - t_0 | T_2 > t_0, T_1 > t_0)}{Q_\tau(T_2 - t_0 | T_2 > t_0, T_1 \leq t_0)}, \quad \tau \in (0, 1), \quad t_0 > 0,$$

where $Q_\tau(Y|A) \equiv \inf\{t: \Pr(Y \leq t|A) \geq \tau\}$ denotes the τ -th quantile of Y given condition A holds. Like the cross-ratio function, $CQRR(\tau; t_0)$ can capture a dynamic relation between the nonterminal and the terminal event. By adopting the quantile residual time, instead of the hazard function, to evaluate the progression of the terminating event, $CQRR(\tau; t_0)$ does not require smoothing for nonparametric estimation and moreover offers straightforward interpretations. For example, $CQRR(\tau; t_0) > 1$ (or < 1) indicates that the nonterminal event occurring before t_0 may be associated with a faster (or slower) progression to subsequent terminal event. For further interpretation convenience, one can assess $CQRR(\tau; t_0)$ in the logarithm scale, which is

$$LCQRR(\tau; t_0) = \log \left\{ \frac{Q_\tau(T_2 - t_0 | T_2 > t_0, T_1 > t_0)}{Q_\tau(T_2 - t_0 | T_2 > t_0, T_1 \leq t_0)} \right\}, \quad \tau \in (0, 1), \quad t_0 > 0.$$

The larger the magnitude of $LCQRR(\tau; t_0)$, the bigger the impact of having the occurrence of the nonterminal event on the residual time of the terminal event. When T_1 and T_2 are independent, $LCQRR(\tau; t_0) = 0$ for $\tau \in (0, 1)$ and $t_0 > 0$.

This paper concerns the estimation and inference of $LCQRR(\tau; t_0)$ for semi-competing risks data in the presence of left truncation. Left truncation is a common complication in observational studies. For example, in the Denmark diabetes registry study (Andersen et al., 1993), a semi-competing risks structure is formed by time to diabetic nephropathy (DN) (corresponding to T_1) and time to death (corresponding to T_2). Left truncation is present in this semi-competing risks setting because patients who had died before study enrollment were excluded. This means that (T_1, T_2) is observable only when T_2 is greater than L , which is the left truncation time standing for time to study entry. Yang and Peng (2016) studied the estimation of $LCQRR(\tau; t_0)$ for such left truncated semi-competing risks data under the assumption that $C - L$ is independent of L , where C denotes time to random censoring (to T_1 and T_2). Their method (hereafter referred to as YP method) is suitable for many retrospective observational studies, for example, studies that collect event time data from reviewing medical records over a specified calendar year period and thus imply a prespecified $C - L$, which is independent of L . However, assuming the independence of $C -$

L and L can be problematic in many other types of observational studies. For instance, in a prospective followup study, where the random censoring is resulted from a common data collection cut-off date, given subjects often enter the study at different times, a later study entry (likely corresponding to a larger L) may be suggestive of a shorter follow-up period (i.e. smaller $C - L$). In this case, it is more reasonable to expect that $C - L$ is negatively associated with L (than assuming the independence between $C - L$ and L). When the independence of $C - L$ and L is violated, the YP estimator can be severely biased, as evidenced by the simulation results in Section 4.1.

The main thrust of this work is to propose a new estimator of $LCQRR(\tau; t_0)$ which does not require the strong assumption described above. Following Yang and Peng (2016)'s strategy, we formulate $LCQRR(\tau; t_0)$ within a quantile regression framework and adapt existing techniques for quantile regression. An advantage of this strategy is about facilitating a simple extension to accommodate covariates. When constructing the proposed estimating equation, we employ the idea of inverse probability censoring weighting (IPCW) to correct the bias induced by truncation and censoring. To implement the weighting scheme, we derive a new estimator of a bivariate probability of (L, C) with left truncated semi-competing risks data. We study the asymptotic properties of the resulting estimator of $LCQRR(\tau; t_0)$ and develop inference procedures accordingly.

In Section 2, we present the proposed estimator as well as the asymptotic studies and inference procedures. In Section 3, we discuss an useful extension of our proposals in Section 2, which enables us to account for covariates when evaluating $LCQRR(\tau; t_0)$. We conduct extensive simulation studies to evaluate the performance of our proposal and illustrate the proposed method by an application to a Denmark Diabetic registry dataset; please see Section 4. In Section 5, we conclude this paper with a few remarks.

2 The Proposed Estimator of $LCQRR(\tau; t_0)$

2.1 Data and notation

Let T_1 , T_2 and C denote time to nonterminal event, time to terminal event and time to random censoring respectively. In the absence of left truncation, semi-competing risks data consists of (X, Y, δ, η) , where $X = \min(T_1, T_2, C)$, $Y = \min(T_2, C)$, $\delta = \mathbb{I}(T_1 < Y)$ and $\eta = \mathbb{I}(T_2 < C)$.

Left truncation arises when data are observable only when $Y > L$, where L represents time to truncation. In this case, the observed data consist of $\{(X_i^*, Y_i^*, \delta_i^*, \eta_i^*, L_i^*)\}_{i=1}^n$, which are n independent and identically distributed replicates of $(X^*, Y^*, \delta^*, \eta^*, L^*)$ that follows the conditional distribution of (X, Y, δ, η, L) given $Y > L$.

In the rest of the paper, we assume random censoring and truncation. That is, (L, C) is independent of (T_1, T_2) . In addition, we define additional notation, $A^*(t_0) = (1, \mathbb{I}(X^* > t_0))^T$, $\tilde{A}^*(t_0) = (1, \mathbb{I}(T_1^* > t_0))^T$, $A(t_0) = (1, \mathbb{I}(X > t_0))^T$ and $\tilde{A}(t_0) = (1, \mathbb{I}(T_1 > t_0))^T$. For a vector $\mathbf{v}$, we use $\mathbf{v}^{(l)}$ to denote the l th component of $\mathbf{v}$.

2.2 Estimation

Following Yang and Peng (2016)'s strategy, we formulate $LCQRR(\tau; t_0)$ under a working quantile residual time regression model,

$$Q_\tau(T_2 - t_0 \mid T_2 > t_0, I(T_1 > t_0)) = \exp \{ \tilde{\mathbf{A}}(t_0)^T \boldsymbol{\beta}_0(\tau, t_0) \}, \quad (1)$$

where $\boldsymbol{\beta}_0(\tau, t_0) = (\boldsymbol{\beta}_0^{(1)}(\tau, t_0), \boldsymbol{\beta}_0^{(2)}(\tau, t_0))^T$ is a 2×1 vector of unknown coefficients. The rationale is that model (1) is equivalent to specifying $\log Q_\tau(T_2 - t_0 \mid T_2 > t_0, T_1 \leq t_0) = \boldsymbol{\beta}_0^{(1)}(\tau, t_0)$ and $LCQRR(\tau; t_0) = \boldsymbol{\beta}_0^{(2)}(\tau, t_0)$. Without imposing any parametric assumptions on $\boldsymbol{\beta}_0^{(1)}(\cdot)$ and $\boldsymbol{\beta}_0^{(2)}(\cdot)$, model (1) provides an alternative platform to study the nonparametric estimation of $LCQRR(\tau; t_0)$.

Estimating $\boldsymbol{\beta}_0^{(2)}(\tau, t_0)$ (and thus $LCQRR(\tau; t_0)$) is complicated by the presence of left truncation and right censoring in the semi-competing risks setting. This is because both the response T_2 and the covariate $I(T_1 > t_0)$ of model (1) are subject to incomplete observations. To tackle this problem, our strategy is to appropriately weigh the contributions of subjects who have complete information on $(\min(T_1, T_2), T_2)$ with $T_2 > t_0$.

Specifically, we consider the subject subset $\mathcal{D} = \{i: Y_i^* > t_0, L_i^* \leq t_0, \text{ and } \eta_i^* = 1\}$. First note that

$$\begin{aligned} & E \{ I\{L^* \leq t_0\} I(Y^* > t_0) \eta^* \mathbf{A}^*(t_0) \{ I[\log(Y^* - t_0) \leq \mathbf{A}^{*T}(t_0) \mathbf{b}] - \tau \} \} \\ &= E \left\{ \frac{I(T_2 > t_0) \tilde{\mathbf{A}}(t_0) \{ I[\log(T_2 - t_0) \leq \tilde{\mathbf{A}}^T(t_0) \mathbf{b}] - \tau \} I(L \leq t_0, C > T_2)}{\alpha} \right\}, \end{aligned} \quad (2)$$

where $\alpha = P(Y > L)$. Under the assumption that (L, C) is independent of (T_1, T_2) , we apply the technique of IPCW and evaluate the expectation in (2) by first conditioning it on (T_1, T_2) . This suggests using an inverse weight $D(t_0, Y^*)^{-1}$, where $D(s, t) = \alpha^{-1} P(L \leq s, C > t)$. Such a weighting scheme is justified by the result,

$$\begin{aligned}
& E \left\{ \frac{I(L^* \leq t_0)I(Y^* > t_0)\eta_i^*}{D(t_0, Y^*)} \mathbf{A}^*(t_0) \{I[\log(Y^* - t_0) \leq \mathbf{A}^{*T}(t_0)\boldsymbol{\beta}_0(\tau, t_0)] - \tau\} \right\} \quad (3) \\
& = E \left\{ I(T_2 > t_0) \tilde{\mathbf{A}}(t_0) \{I[\log(T_2 - t_0) \leq \tilde{\mathbf{A}}^T(t_0)\boldsymbol{\beta}_0(\tau, t_0)] - \tau\} \right. \\
& \quad \times \left. \frac{E[I(L \leq t_0, C > T_2) | T_1, T_2]}{\alpha D(t_0, T_2)} \right\} \\
& = E \left\{ I(T_2 > t_0) \tilde{\mathbf{A}}(t_0) \{I[\log(T_2 - t_0) \leq \tilde{\mathbf{A}}^T(t_0)\boldsymbol{\beta}_0(\tau, t_0)] - \tau\} \right\} = 0,
\end{aligned}$$

where the last equality in (3) follows from model (1); a detailed proof for (3) is provided in Appendix 6.1. In the event $\mathcal{D}$ targeted by equation (3), $I(T_1 > t_0)$ and $I(T_2 > t)$ with $t > t_0$ can be fully determined under the censoring and truncation scheme considered here, and consequently sufficient information is available to estimate the residual quantiles, $Q_\tau(T_2 - t_0 | T_2 > t, T_1 > t_0)$ and $Q_\tau(T_2 - t_0 | T_2 > t_0, t_1 - t_0)$, involved in $LCQRR(\tau; t_0)$. Following the rationale underlying IPCW, the weight $D(t_0, Y^*)$ plays a role in adjusting for the sampling bias from focusing on $\mathcal{D}$.

In light of equation (3), we propose to estimate $\boldsymbol{\beta}_0(\tau, t_0)$ by solving the following estimating equation for $\mathbf{b}$:

$$S_n(\mathbf{b}, \tau, t_0) = \mathbf{0}, \quad (4)$$

where $S_n(\mathbf{b}, \tau, t_0)$ equals

$$n^{-1/2} \sum_{i=1}^n \frac{I(L_i^* \leq t_0)I(Y_i^* > t_0)\eta_i^*}{\hat{D}(t_0, Y_i^*)} \mathbf{A}_i^*(t_0) \{I[\log(Y_i^* - t_0) \leq \mathbf{A}_i^{*T}(t_0)\mathbf{b} - \tau]\}.$$

Here, $\hat{D}(s, t)$ denotes a reasonable estimator of $D(s, t)$. The estimator obtained from solving equation (4) is denoted by $\hat{\boldsymbol{\beta}}(\tau, t_0)$.

Remark: With the additional assumptions that $L < C$ and $O \equiv C - L$ is independent of L , Yang and Peng (2016) employed a different inverse weight, $G_1(Y^* - L^*)^{-1}$, where $G_1(t) = P(O > t)$. This weight was derived by rearranging $I(L - t_0, C > T_2)$ as $I(L - t_0)I(O > T_2 - L)$ and then taking the expectation in (2) conditional on (T_1, T_2, L) . Given O is independent of (T_1, T_2, L) , $G_1(t)$ can be straightforwardly estimated by a Kaplan-Meier estimator based on $\{(Y_i^* - L_i^*, 1 - \eta_i^*)\}_{i=1}^n$.

To estimate $LCQRR(\tau; t_0)$, the remaining task is to obtain the weights, $\hat{D}(t_0, Y_i^*)$, in estimating equation (4). Note that estimating equation (4) only uses the subset satisfying $Y_i^* > t_0$. Thus it suffices to derive the estimator of $D(s, t)$ for $s < t$ rather than over the whole domain.

Let $G(s) = P(L^* \leq s < C)$, $S(t|s) = P(C > t | L^* \leq s < C)$ and $S_{T_2}(s) = P(T_2 > s)$. By the definition of $D(s, t)$, we have $D(s, t) \doteq \alpha^{-1} P(L^* \leq s, C > t) = \alpha^{-1} G(s)S(t|s)$ for $s < t$. We also note that

$$\frac{P(L^* \leq s < Y^*)}{S_{T_2}(s)} = \frac{P(L \leq s < Y)}{P(L < Y)P(T_2 > s)} = \frac{P(L \leq s < C)}{P(L < Y)} = \alpha^{-1} G(s),$$

where the second equality follows from $(L, C) \perp T_2$. It is implied by these facts that

$$D(s, t) = P(L^* \leq s < Y^*)S(t | s)/S_{T_2}(s) \quad \text{for } s < t.$$

This result suggests a plug-in estimator of $D(s, t)$, with $P(L^* \leq s < Y^*)$, $S(t|s)$, and $S_{T_2}(s)$ replaced by their respective estimators.

Along this direction, we can first estimate $P(L^* \leq s < Y^*)$ by its empirical counterpart, $n^{-1} \sum_{i=1}^n I(L_i^* \leq s < Y_i^*)$. Since T_2 is only subject to random right censoring and left truncation, we can readily estimate $S_{T_2}(s)$ by Lyden-Bell (1971)'s estimator,

$$\hat{S}_{T_2}(s) = \prod_{Y_j^* \leq s} \left\{ 1 - \frac{\sum_{i=1}^n I(Y_i^* = Y_j^*, \eta_i^* = 1)}{\sum_{i=1}^n I(L_i^* \leq Y_j^* \leq Y_i^*)} \right\}.$$

For $S(t|s)$, we propose a Nelson-Aalen type estimator tailored to the left-truncated semi-competing risks data. Let $\lambda(t|s) = \lim_{h \rightarrow 0} P(t - C < t + h | L^* \leq s < C, C - t)/h$ and $\Lambda(t | s) = \int_s^t \lambda(u | s) du$. For $s < t$, it is easy to show that

$$\Lambda(t | s) = \int_s^t \frac{W_s(du)}{C_s(u)},$$

where $W_s(u) = P(L^* \leq s < Y^* | u, \eta^* = 0)$ and $C_s(u) = P(L^* \leq s < u | Y^*)$. Thus, an estimator for $\Lambda(t|s)$ can take the form as

$$\Lambda_n(t | s) \equiv \int_s^t \frac{W_{n,s}(du)}{C_{n,s}(u)}$$

where $W_{n,s}(u) = \frac{1}{n} \sum_{i=1}^n I(L_i^* \leq s < Y_i^* \leq u, \eta_i^* = 0)$ and $C_{n,s}(u) = \frac{1}{n} \sum_{i=1}^n I(L_i^* \leq s < u \leq Y_i^*)$.

Given that $\mathcal{S}(t|s) = \exp\{-\Lambda(t|s)\}$, we derive an estimator of $\mathcal{S}(t|s)$ as

$$\hat{S}(t|s) = \exp\{-\hat{\Lambda}_n(t|s)\}.$$

Under some regularity conditions, we can show the uniform consistency of $\hat{D}(s, t)$ for $s < t$ (see Appendix 6.2).

Finally, we obtain an estimator of $D(s, t)$,

$$\hat{D}(s, t) = \frac{1}{n} \sum_{i=1}^n \frac{I(L_i^* \leq s < Y_i^*) \hat{S}(t|s)}{\hat{S}_{T_2}(s)}, \quad s < t.$$

Plugging $\hat{D}(s, t)$ into (4), we can readily solve equation (4) by following the same lines of Yang and Peng (2016). Given the monotonicity of equation (4) (Fygenson and Ritov, 1994), we can transform its solution finding to locating the minimizer of the convex function $U_n(\mathbf{b}, \tau, t_0)$ given by

$$U_n(\mathbf{b}, \tau, t_0) = \sum_{i=1}^n I(L_i^* \leq t_0) I(Y_i^* > t_0) \eta_i^* \left| \frac{\log(Y_i^* - t_0)}{\hat{D}(t_0, Y_i^*)} - \mathbf{b}^T \frac{A_i^*(t_0)}{\hat{D}(t_0, Y_i^*)} \right| + \left| M - (2\tau - 1) \mathbf{b}^T \sum_{i=1}^n I(L_i^* \leq t_0) I(Y_i^* > t_0) \eta_i^* \frac{A_i^*(t_0)}{\hat{D}(t_0, Y_i^*)} \right|,$$

where M is a sufficiently large positive number. The purpose of having a sufficiently large

positive M is to make the term, $M - (2\tau - 1) \mathbf{b}^T \sum_{i=1}^n I(L_i^* \leq t_0) I(Y_i^* > t_0) \eta_i^* \frac{A_i^*(t_0)}{\hat{D}(t_0, Y_i^*)}$, always

positive so that the derivative of $U_n(\mathbf{b}, \tau, t_0)$ with respect to $\mathbf{b}$ is proportional to the proposed estimating function $S_n(\mathbf{b}, \tau, t_0)$. This shows that a feasible solution to estimating equation (4) should correspond to a minimizer of $U_n(\mathbf{b}, \tau, t_0)$ that makes

$M - (2\tau - 1) \mathbf{b}^T \sum_{i=1}^n I(L_i^* \leq t_0) I(Y_i^* > t_0) \eta_i^* \frac{A_i^*(t_0)}{\hat{D}(t_0, Y_i^*)}$ well above 0 (e.g. > 10). Therefore, the

selection of M (as long as it is reasonably large) is not expected to affect the actual estimation and computation.

2.3 Asymptotic results

It suffices to derive the asymptotic properties of $\hat{\beta}(\tau, t_0)$, given that the proposed estimator of $LCQRR(\tau; t_0)$ is equal to $\hat{\beta}^{(2)}(\tau, t_0)$. Throughout this paper, we assume T_1, T_2, L and C are

continuous random variables. For a random variable K , define $a_K = \inf\{k: P(K \leq k) > 0\}$ and $b_K = \sup\{k: P(K \leq k) < 1\}$. We adopt the following regularity conditions:

- C1** $a_L < a_Y, b_L < b_Y$.
- C2** $\inf_{s \in (a_L^*, b_Y^*], u \in (s, b_Y^*]} P(L^* \leq s < u \leq Y^*) > 0$.
- C3** (i) $\beta_0(\tau, t_0)$ is Lipschitz continuous for $\tau \in [\tau_L, \tau_U]$ and $t_0 \in [t_L, t_U]$; (ii) $f(t|\tilde{A}(t_0))$ is continuous and bounded above uniformly in t, t_0 and $\tilde{A}(t_0)$, where $f(t|\tilde{A}(t_0)) = dF(t|\tilde{A}(t_0))/dt$ and $F(t|\tilde{A}(t_0)) = E\{I(T_2 \leq t)|\tilde{A}(t_0)\}$.
- C4** For some $\rho_0 > 0$ and $c_0 > 0$, $\inf_{b \in B(\rho_0), t_0 \in [t_L, t_U]} \text{eigmin } H(b, t_0) \geq c_0$, where $B(\rho) = \{b \in R^2: \inf_{\tau \in [\tau_L, \tau_U], t_0 \in [t_L, t_U]} \|b - \beta_0(\tau, t_0)\| \geq \rho\}$, $H(b, t_0) = E[\tilde{A}(t_0)^{\otimes 2} f(t_0 + \exp(\tilde{A}^T(t_0)b)|\tilde{A}^T(t_0)) \exp(\tilde{A}^T(t_0)b)]$, and eigmin stands for the minimum eigenvalue of a matrix. Here $\|\cdot\|$ is the Euclidean norm and $u^{\otimes 2} = uu^T$ for a vector u .

We then have the following theorems:

Theorem 1—Under conditions C1–C4,

$$\lim_{n \rightarrow \infty} \sup_{\tau \in [\tau_L, \tau_U], t_0 \in [t_L, t_U]} \|\hat{\beta}(\tau, t_0) - \beta_0(\tau, t_0)\| \rightarrow_p 0,$$

where $0 < \tau_L < \tau_U < 1$, and t_L and t_U are interior points of the support of X^* .

Theorem 2—Under conditions C1–C4, $\sqrt{n}\{\hat{\beta}(\tau, t_0) - \beta_0(\tau, t_0)\}$ weakly converge to a mean zero Gaussian process with covariance matrix given by

$$\Phi(\tau', t'_0, \tau, t_0) = H\{\beta_0(\tau', t'_0), t'_0\}^{-1} E\{\xi_1(\tau', t'_0)\xi_1(\tau, t_0)^T\} [H\{\beta_0(\tau, t_0), t_0\}^{-1}]^T,$$

where the formal definition of $\xi_1(\tau, t_0)$ is provided in Appendix, $\tau, \tau' \in [\tau_L, \tau_U]$ and $t_0, t'_0 \in [t_L, t_U]$. Here $0 < \tau_L < \tau_U < 1$, and t_L and t_U are interior points of the support of X^* .

Theorem 1 indicates the uniform consistency of the proposed estimator for $LCQRR(\tau; t_0)$ in $\tau \in [\tau_L, \tau_U]$ and $t_0 \in [t_L, t_U]$. Theorem 2 presents a closed form expression for the asymptotic distribution of the proposed estimator of $LCQRR(\tau; t_0)$. The proofs of Theorems 1 and 2 follow similar lines of Yang and Peng (2016). The main extra work in our proofs is to establish the asymptotic properties of the new weight function $\hat{D}(s, t)$ with $s < t$, including its uniform consistency and weak convergence along with the derivation of the influence functions. The detailed proofs of Theorem 1 and 2 are provided in the Appendix.

2.4 Inference

For inference on $\hat{\beta}(\tau, t_0)$, we use bootstrapping procedures, given the complexity in the asymptotic distribution of $\hat{\beta}(\tau, t_0)$ shown in the proof of Theorem 2. Denote $\beta^*(\tau, t_0)$ as the

bootstrap estimator. It can be shown that the limit distribution of $n^{1/2}\{\hat{\beta}^*(\tau, t_0) - \hat{\beta}(\tau, t_0)\}$ conditionally on the observed data and the limit unconditional distribution of $n^{1/2}\{\hat{\beta}(\tau, t_0) - \beta_0(\tau, t_0)\}$ are the same. Therefore, one can first obtain a large number of realizations of $n^{1/2}\{\hat{\beta}^*(\tau, t_0) - \hat{\beta}(\tau, t_0)\}$ by repeatedly resampling with replacement from the observed data, and then use their empirical covariances or percentiles to estimate the asymptotic covariance of $\hat{\beta}(\tau, t_0)$ and the 95% Wald-type confidence interval for $\beta_0(\tau, t_0)$. We can also derive a closed form variance estimator for $\hat{\beta}(\tau, t_0)$ by following the lines of Yang and Peng (2016). The detailed procedure is described in Appendix (see Section 6.4).

We can also conduct second-stage inferences to explore the dynamic pattern of $LCQRR(\tau; t_0)$. For example, we can summarize $LCQRR(\tau; t_0)$ over $t_0 \in [t_L, t_U]$ by

$$\Omega_\tau = \frac{1}{t_U - t_L} \int_{t_L}^{t_U} \beta_0^{(2)}(\tau, t_0) dt_0, \text{ which may be consistently estimated by}$$

$$\hat{\Omega}_\tau = \frac{1}{t_U - t_L} \int_{t_L}^{t_U} \hat{\beta}^{(2)}(\tau, t_0) dt_0. \text{ Bootstrapping can be used to estimate the asymptotic variance of } \hat{\Omega}_\tau. \text{ A Wald-type test can be constructed based on } \hat{\Omega}_\tau \text{ for testing the null hypothesis } H_{01}: LCQRR(\tau; t_0) = 0, t_0 \in [t_L, t_U]. \text{ Similar results can be obtained for the overall summary and testing of } LCQRR(\tau; t_0) \text{ over } \tau \in [\tau_L, \tau_U], \text{ corresponding to } \Omega_{t_0} = \frac{1}{\tau_U - \tau_L} \int_{\tau_L}^{\tau_U} \beta_0^{(2)}(\tau, t_0) d\tau, \text{ and } H_{03}: LCQRR(\tau; t_0) = 0, \tau \in [\tau_L, \tau_U] \text{ respectively.}$$

Evaluating the constancy of $LCQRR(\tau; t_0)$ over t_0 or τ can also be of practical interest. To this end, one may consider a null hypothesis taking the form, $H_{02}: LCQRR(\tau; t_0) = C_\tau, t_0 \in [t_L, t_U]$, where C_τ is an unspecified constant over t_0 and may change with τ . A test statistic for H_{02} may be constructed based on $\Gamma_\tau = \sqrt{n} \{ \int_{t_L}^{t_U} \Xi(\tau, t_0) \hat{\beta}^{(2)}(\tau, t_0) dt_0 - \hat{\Omega}_\tau \}$, where $\Xi(\tau, t_0)$ is a known non-constant weight function satisfying $\int_{t_L}^{t_U} \Xi(\tau, t_0) dt_0 = 1$. We can show that the limit distribution of Γ_τ under H_{02} is normal with mean 0. A consistent variance estimate for Γ_τ can be obtained through bootstrapping. This would render a Wald-type test for H_{02} . A similar testing procedure can be developed for testing the constancy over $t_0 \in [t_L, t_U]$, $H_{04}: LCQRR(\tau; t_0) = C_{t_0}, \tau \in [\tau_L, \tau_U]$.

3 An extension to adjust for covariates

In real applications, it is often of interest to investigate whether semi-competing risks dependence varies according to subjects' characteristics, such as gender and age. In this subsection, we study an extension that allows us to address such a question. Specifically, let $\tilde{\mathbf{Z}}$ denote a $p \times 1$ vector of covariates. We formulate covariate effects on $LCQRR(\tau; t_0)$ via a linear regression model:

$$LCQRR(\tau; t_0 | \tilde{\mathbf{Z}}) = \tilde{\mathbf{Z}}^T \boldsymbol{\alpha}_0(\tau, t_0), \quad (5)$$

where $LCQRR(\tau; t_0 | \tilde{\mathbf{Z}}) = \log \left[\frac{Q_\tau(T_2 - t_0 | T_2 > t_0, T_1 > t_0, \tilde{\mathbf{Z}})}{Q_\tau(T_2 - t_0 | T_2 > t_0, T_1 \leq t_0, \tilde{\mathbf{Z}})} \right]$, $\tilde{\mathbf{Z}} = (1, \tilde{\mathbf{Z}}^T)^T$ and $\alpha_0(\tau, t_0)$ are coefficients representing covariate effects on $LCQRR(\tau; t_0)$.

To tackle model (5), following the strategy of Yang and Peng (2016), we consider a quantile residual time regression model,

$$Q_\tau(T_2 - t_0 | T_2 > t_0, I(T_1 > t_0), \tilde{\mathbf{Z}}) = \exp \{ \mathbf{Z}^T(t_0) \boldsymbol{\gamma}_0(\tau, t_0) \} \quad (6)$$

where $\mathbf{Z}(t_0) = (1, I(T_1 > t_0), \tilde{\mathbf{Z}}^T, \tilde{\mathbf{Z}}^T I(T_1 > t_0))^T$. It is easy to show that model (6) implies (5) with $\alpha_0(\tau, t_0) = (\boldsymbol{\gamma}_0^{(2)}(\tau, t_0), \boldsymbol{\gamma}_0^{(3+p):(2+2p)}(\tau, t_0))$, where $\mathbf{v}^{a:b}$ denotes the a th to b th components of vector $\mathbf{v}$. Models (6) and (5) are equivalent when there only involve discrete covariates. Model (6) imposes mild additional assumptions on $Q_\tau(T_2 - t_0 | T_2 > t_0, T_1 > t_0, \tilde{\mathbf{Z}})$ and $Q_\tau(T_2 - t_0 | T_2 > t_0, T_1 \leq t_0, \tilde{\mathbf{Z}})$ beyond (5) when there are continuous covariates.

The estimation for $\alpha_0(\tau, t_0)$ is thus transformed to the problem of estimating $\boldsymbol{\gamma}_0(\tau, t_0)$. Suppose the observed data consist of $\{(X_i^*, Y_i^*, \delta_i^*, \eta_i^*, L_i^*, \tilde{\mathbf{Z}}_i^*)\}_{i=1}^n$, where $\tilde{\mathbf{Z}}_i^*$ follows the conditional distribution of $\tilde{\mathbf{Z}}$ given $Y > L$. Define

$\mathbf{K}^*(t_0) = (1, I(X_i^* > t_0), \tilde{\mathbf{Z}}_i^{*T}, \tilde{\mathbf{Z}}_i^{*T} I(X_i^* > t_0))^T$. Under the assumption that (L, C) is independent of $(T_1, T_2, \tilde{\mathbf{Z}})$, we propose to estimate $\boldsymbol{\gamma}_0(\tau, t_0)$ by solving the following estimating equation for $\mathbf{r} \in \mathbb{R}^{2+2p}$:

$$S_n(\mathbf{r}, \tau, t_0) = \mathbf{0},$$

where

$$S_n(\mathbf{r}, \tau, t_0) = n^{-1/2} \sum_{i=1}^n \frac{I(L_i^* \leq t_0) I(Y_i^* > t_0) \eta_i^*}{\hat{D}(t_0, Y_i^*)} \mathbf{K}_i^*(t_0) \{ I[\log(Y_i^* - t_0) \leq \mathbf{K}_i^{*T}(t_0) \mathbf{r}] - \tau \}.$$

We can establish asymptotic properties and develop inference procedures that resemble those presented in Section 2.

4 Numerical Studies

4.1 Simulations

We conduct extensive simulation studies to evaluate the finite sample performances of the proposed estimator. Specifically, we let T_i follow a Weibull(α_i, λ_i) distribution (i.e. $P(T_i > x) = \exp(-\lambda_i x^{\alpha_i})$), $i = 1, 2$. We generate (T_1, T_2) from a gamma frailty model,

$$P(T_1 > x, T_2 > y) = [P(T_1 > x)]^{1-\theta} + [P(T_2 > y)]^{1-\theta} - 1]^{1/(1-\theta)}.$$

The truncation time $L = r \times L_0$, where r is a random variable following Bernoulli distribution with probability p , and L_0 is a positive random variable that is independent of r . Such a truncation scenario mimics the Denmark diabetes registry study, where the distribution of L has a point mass at 0. We generate the censoring time C as $L + D_0$, where D_0 is a L -dependent positive-valued random variable.

Our simulations are conducted under two scenarios and each scenario consists of three setups corresponding to three different θ values, 1, 2 and 3 (equivalently, Kendall's τ values, 0, 1/3, and 1/2), which reflects independence, moderate positive association and strong positive association respectively. In Scenario 1, the truncation rate $P(Y < L)$ is set to be low to moderate and equals 0.3. The dependent censoring rate $P(\delta^* = 0, \eta^* = 1)$ is set to be moderate to high, close to 0.36. Scenario 2 involves a moderate to high level of truncation with $P(Y < L) = 0.45$ and a low to moderate level of dependent censoring around 0.2. In both scenarios, the proportion of zero truncation time $P(L^* = 0)$ equals 0.2. Details about the choice of (T_1, T_2, p, L_0, D_0) in each setup as well as corresponding censoring proportions are given in Table 1.

Under each setup, we implement the proposed methods on 1000 simulated datasets with sample size $n = 400$, where M is set as 10^7 . For bootstrapping-based inference, we set the resampling size as 250. The empirical bias (EmpBias), empirical standard error (EmpSE) and average estimated standard error based on bootstrapping (EstSE) as well as the empirical coverage rate of the 95% Wald-type confidence intervals for the proposed estimator of $LCQRR(\tau; t_0)$, are reported under different combinations of (θ, τ, t_0) , where $\tau = 0.25, 0.5, 0.75$, and t_0 are at grid over an interval $[t_L, t_U]$ with grid size 0.005. In Scenario 1, we set $t_L = 0.65$ and $t_U = 1.30$. In Scenario 2, we set $t_L = 0.62$ and $t_U = 1.20$. Figure 1 presents the results for Scenario 1, showing that the proposed estimator of $LCQRR(\tau; t_0)$ performs well with moderate sample size. The point estimates have small biases. The bootstrapping-based standard error estimates closely match their empirical counterparts, and the Wald-type confidence intervals based on normal approximation provide satisfactory empirical coverage. For comparison purpose, we also provide the empirical bias of the YP estimator, which requires the independence of L and $C - L$. It is shown that, under our scenario that $C - L$ depends on L , the YP approach can lead to substantial biases, in particular in cases with larger θ and t_0 values. We have similar findings in Figure 2, which presents the simulation results for Scenario 2.

We also evaluate the performance of the proposed second-stage inference for $LCQRR(\tau; t_0)$ over $t_0 \in [t_L, t_U]$ with fixed τ . We consider three τ values, 0.25, 0.5, 0.75, and the same interval $[t_L, t_U]$ specified before. We choose the weight function $\Xi(\tau, t_0) = 2\mathbb{I}_{t_0} \in [t_L, t_U]/2 \times (t_U - t_L)$. Table 2 summaries the EmpBias, EmpSE and EstSE of $\hat{\Omega}_\tau$ and the empirical rejection rates (EmpRR) for the Wald tests for H_{01} and H_{02} . It shows that for both scenarios, the empirical bias of $\hat{\Omega}_\tau$ are small and the average estimated standard errors agree very well with corresponding empirical standard errors. The test for either H_{01} or H_{02} appear to have

empirical sizes (when $\theta = 1$) close to the nominal levels. The proposed test has a good power for testing H_{01} (when $\theta = 2$ and 3). The power for the constancy is not high but is expected to increase with a larger departure from coefficient constancy.

Similarly, we examine the second-stage inferences over $[\tau_L, \tau_U]$ with fixed t_0 . We consider $t_0 = 0.7, 1.0, 1.2$ for Scenario 1, and $t_0 = 0.7, 0.9, 1.1$ for Scenario 2. We set $[\tau_L, \tau_U] = [0.15, 0.85]$, choose grid size 0.001, and let $\Xi(\tau, t_0) = 2\mathbb{I}[\tau - (\tau_L + \tau_U)/2]/(\tau_U - \tau_L)$. Results are presented in Table 3, and suggest similar findings to those from Table 2.

Following one referee's suggestion, we also conduct simulations for scenarios where $C - L$ and L are independent. The simulation results (unreported here) show that the new estimator proposed in this work has similar finite-sample performance (such as empirical bias and empirical standard deviation) to the existing YP estimator when the independence of $C - L$ and L holds. Nevertheless, the YP method has some computational advantage. For example, in one simulation setup, the computation time ratio of the new approach to the YP method ranges from 3.3 to 6.6 with mean = 5.2 and median = 5.2. The faster computation of the YP approach can be a useful feature in the analysis of large datasets when the independence of $C - L$ and L is plausible.

4.2 Denmark Diabetes Registry Data Analysis

The Denmark diabetes registry study (Andersen et al., 1993) is a prospective cohort study of insulin-dependent diabetes patients who were diagnosed prior to age 31 and accrued between 1933 and 1972. At study entry, patients' age at diabetes diagnosis and age at the onset of diabetic nephropathy were recorded. All patients in the registry were followed from study entry until death, emigration or December 31, 1984. With the time origin set as diabetes diagnosis, time to diabetic nephropathy (DN), which corresponds to T_1 , and time to death, which corresponds to T_2 , formed a semi-competing risks structure. In this set-up, L is time to study entry which ranges between 1933 and 1972, and C is time to emigration or December 31, 1984. This prospective follow-up scheme suggests a negative association between $C - L$ and L . This conjecture is endorsed by an ad-hoc Cox regression of $C^* - L^*$ on L^* , which produces a negative coefficient for L^* and a small p value 0.001. The goal of this analysis is to quantify the relationship between DN and death by using the cross quantile residual ratio measured in logarithm scale, $LCQRR(\tau; t_0)$. Applying the proposed method is expected to enhance the statistical validity of the results on $LCQRR(\tau; t_0)$.

In this analysis, we focus on a subcohort of patients who had diabetes onset age greater than 19 in order to reduce the population heterogeneity as the disease mechanism of childhood diabetes may be different from that of adult diabetes. This subcohort includes 854 patients, among which, 181(21%) subjects experienced DN and 239(28%) died during the study. Approximately 28% patients had diabetic onset at the study entry. In this analysis, the time origin was diabetes diagnosis, and event times were measured in years since diagnosis.

We fit model (1) to the dataset and adopt $M = 10^7$ as in the simulations. To ensure reasonable sample sizes accumulated for strata defined by $\mathbb{I}(X^* > t_0)$, we restrict t_0 to be within $[12, 28)$. Table 4 presents estimated $LCQRR(\tau; t_0)$, the corresponding 95% pointwise Wald-type bootstrapping confidence interval with resampling size of 500 and p -value for

testing $LCQRR(\tau; t_0) = 0$ at several combinations of (τ, t_0) , where $\tau = 0.25, 0.5$ and $t_0 = 12, 15, 18, 21, 25$, and 27 . Here, $t_0 = 15$ and 21 are the 25th and 50th empirical quantile of time to DN respectively. We see that for either fixed τ , the estimated $LCQRR(\tau; t_0)$ from our proposed method is generally significantly positive. This observation is consistent with the common belief that DN is a diabetes progression landmark, positively associated with mortality. This is also confirmed by our formal test for H_{01} , which yields p-values < 0.001 . We note that the difference between $LCQRR(\tau; t_0)$ and 0 becomes insignificant when t_0 is greater than 25. This may imply that the late onset of DN in patients who has lived long since diabetes diagnosis has little prognostic value for residual survival time. For fixed τ , the estimated $LCQRR(\tau; t_0)$ appears to have a decreasing trend over t_0 , possibly indicating DN's prognostic power for mortality gradually diminish for long-term survivor of diabetes.

In Table 4, we also provide results obtained from applying the YP approach to the same dataset. In contrast to our proposed estimator, the YP approach results in some quite different estimated $LCQRR(\tau; t_0)$ values. For example, at $(\tau, t_0) = (0.5, 21)$, the YP estimate is small and equals 0.29 with p-value=0.62, showing nonsignificant DN-mortality dependence. In contrast, our proposed method gives the estimated $LCQRR(\tau; t_0)$ equal to 1.15 with p-value=0.004, indicating diabetes patients who were DN-free for over 21 years is associated significantly longer residual survival time (about $3.2 = e^{1.15}$ times) compared to those who had DN within 21 years from diabetes diagnosis. Such a discrepancy is likely caused by the potential dependence between $C-L$ and L in this real dataset. As shown in our simulation studies, a violation of the independence between $C-L$ and L can lead to severely biased estimation in $LCQRR(\tau; t_0)$.

We next study whether diabetes onset age, a continuous covariate, affects the dependence between DN and mortality. We fit model (6) to the data and the coefficient $\gamma_0^{(4)}(\tau, t_0)$ represents the change in $LCQRR(\tau; t_0)$ per one year increase in diabetes onset age. For $\tau = 0.25$ and 0.5 , we estimate $\gamma_0^{(4)}(\tau, t_0)$ at several t_0 values mentioned above. In Table 5, we display the estimated $\gamma_0^{(4)}(\tau, t_0)$ along with corresponding 95% pointwise Wald-type bootstrapping confidence interval and p-value for testing $\gamma_0^{(4)}(\tau, t_0) = 0$. We see that for all τ 's and t_0 's, $\gamma_0^{(4)}(\tau, t_0)$'s are not significantly different from 0. Our overall significance tests for $H_{01}: \gamma_0^{(4)}(\tau, t_0) = 0$ for $t_0 \in [12, 28)$ confirm our observations, yielding p-values, 0.37 and 0.07, corresponding to $\tau = 0.25$ and 0.50 respectively. These suggest that the dependence between DN and mortality measured by $LCQRR(\tau; t_0)$ is quite homogeneous in the subcohort of young adults considered in this analysis.

5 Remarks

In this paper, we study cross quantile residual ratio, a flexible measure proposed by Yang and Peng (2016) for characterizing the dependence between the non-terminal and terminal events in the semi-competing risks setting. Following the strategy of Yang and Peng (2016), we investigate this measure in the logarithm scale, $LCQRR(\tau; t_0)$, by fitting it into the quantile regression framework. As a key contribution of this work, we derive a new

estimator which avoids a strong assumption required by Yang and Peng (2016), i.e. $C - L$ is independent of L . As elaborated in Section 1, this assumption may be problematic in many observational studies. The simulation studies reported in Section 4.1 show that the YP estimator can be considerably biased if this assumption is violated, while the estimator proposed in this paper remains unbiased. This entails the broader applicability of the new estimator in semi-competing risks settings with left truncation.

To use cross quantile residual ratio (or $LCQRR(\tau; t_0)$) in practice, one needs to specify τ and t_0 beforehand according to scientific interests. Common choices of τ are 0.25, 0.5 and 0.75, reflecting below average, average, and above average progression to the terminal event. The choices of t_0 may be time points that landmark the development of the nonterminal event. The specifications of τ and t_0 may also be subject to data adaptive adjustments. For example, the estimation efficacy may be unsatisfactory at small values of t_0 because of a small weight $\hat{D}(t_0, Y_i^*)$ or a small number of observations satisfying $X_i^* \leq t_0$. Based on our numerical experiences, we find that our method generally works well when $\min(n_{t_0,1}, n_{t_0,2}) > 30$, where $n_{t_0,1} = \sum_{i=1}^n I(L_i^* \leq t_0, Y_i^* > t_0, X_i^* > t_0) \eta_i^*$ and $n_{t_0,2} = \sum_{i=1}^n I(L_i^* \leq t_0, Y_i^* > t_0, X_i^* \leq t_0) \eta_i^*$. For a larger τ , we may need $n_{t_0,1}$ and $n_{t_0,2}$ to be larger. These may serve as useful empirical rules to guide the selection of τ and t_0 in real data analysis. Sample R code that implements the proposed method can be found at our website (<http://web1.sph.emory.edu/users/lpeng/Rpackage.html>).

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References

- Andersen PK, Borgan Ø, Gill RD, Keiding N. Statistical Models Based on Counting Processes. New York: Springer; 1993.
- Chen YH. Maximum likelihood analysis of semicompeting risks data with semiparametric regression models. *Lifetime Data Analysis*. 2012; 18:36–57. [PubMed: 21850528]
- Fine JP, Jiang H, Chappell R. On semi-competing risks data. *Biometrika*. 2001; 88:907–919.
- Fygenso M, Ritov Y. Monotone estimating equations for censored data. *Biometrika*. 1994; 22:732–746.
- Ghosh D. Semiparametric inferences for association with semi-competing risks data. *Statistics in Medicine*. 2006; 25:2059–2070. [PubMed: 16196081]
- Gijbels I, Wang J. Strong representations of the survival function estimator for truncated and censored data with applications. *Journal of Multivariate Analysis*. 1993; 47:210–229.
- Hsieh JJ, Wang W, Ding AA. Regression analysis based on semicompeting risks data. *Journal of the Royal Statistical Society Series B*. 2008; 70:3–20.
- Lakhal L, Rivest LP, Abdous B. Estimating survival and association in a semicompeting risks model. *Biometrics*. 2008; 64:180–188. [PubMed: 17645782]
- Lyden-Bell D. Monthly Notices of the Royal Astronomical Society. 1971. A method of allowing for known observational selection in small samples applied to 3cr quasars.
- Oakes D. Bivariate survival models induced by frailties. *Journal of the American Statistical Association*. 1989; 84:487–493.

Peng L, Fine JP. Regression modeling of semi-competing risks data. *Biometrics*. 2007; 63:96–108. [PubMed: 17447934]

Wang M. Estimating the association parameter for copula models under dependent censoring. *Journal of the Royal Statistical Society Series B*. 2003; 65:257–273.

Yang J, Peng L. A new flexible dependence measure for semi-competing risks. *Biometrics*. 2016; 72:770–779. [PubMed: 26916804]

6 Appendix

Define

$$S_n(\mathbf{b}, \tau, t_0) = n^{-1/2} \sum_{i=1}^n \frac{I(L_i^* \leq t_0)I(Y_i^* > t_0)\eta_i^*}{\hat{D}(t_0, Y_i^*)} A_i^*(t_0) \{I[\log(Y_i^* - t_0) \leq A_i^{*T}(t_0)\mathbf{b}] - \tau\},$$

$$S_n^D(\mathbf{b}, \tau, t_0) = n^{-1/2} \sum_{i=1}^n \frac{I(L_i^* \leq t_0)I(Y_i^* > t_0)\eta_i^*}{D(t_0, Y_i^*)} A_i^*(t_0) \{I[\log(Y_i^* - t_0) \leq A_i^{*T}(t_0)\mathbf{b}] - \tau\},$$

$$\mu(\mathbf{b}, \tau, t_0) = n^{-1/2} E\{S_n^D(\mathbf{b}, \tau, t_0)\}.$$

For brevity, we use $\sup_{\mathbf{b}}$, $\sup_{\tau}$ and $\sup_{t_0}$ to denote supremum taken over $\mathbf{b} \in R^2$, $\tau \in [\tau_L, \tau_U]$ and $t_0 \in [t_L, t_U]$, respectively. In the sequel, $o_p^S(n^{-1/2})$ means root n convergence to 0 in probability uniformly on set S .

6.1 Proof of $E\{S_n^D(\beta_0(\tau, t_0), \tau, t_0)\} = 0$

Let $f_{(L, C, T_1, T_2)}(l, c, t_1, t_2)$ denote the joint distribution function of (L, C, T_1, T_2) , and $f_{(L^*, C^*, T_1^*, T_2^*)}(l, c, t_1, t_2)$ denote the joint distribution function of (L^*, C^*, T_1^*, T_2^*) . Note that $f_{(L^*, C^*, T_1^*, T_2^*)}(l, c, t_1, t_2) = \frac{1}{\alpha} f_{(L, C, T_1, T_2)}(l, c, t_1, t_2)$ in the region of $\{(l, c, t_1, t_2): l > t_0, t_2 > t_0, t_2 < c, t_1 > t_0\}$. Based on a fact that $I(Y^* > t_0)\eta^* A^*(t_0) = I(T_2^* > t_0, T_2^* < C^*) \tilde{A}^*(t_0)$, thus we have

$$\begin{aligned}
& E \left\{ \frac{I(L^* \leq t_0)I(Y^* > t_0)\eta^*}{D(t_0, Y^*)} A^*(t_0) \{I[\log(Y^* - t_0) \leq A^{*T}(t_0)\beta_0(\tau, t_0)] - \tau\} \right\} \\
&= E \left\{ \frac{I(L^* \leq t_0)I(T_2^* > t_0, T_2^* < C^*)}{D(t_0, T_2^*)} \tilde{A}^*(t_0) \{I[\log(T_2^* - t_0) \leq \tilde{A}^{*T}(t_0)\beta_0(\tau, t_0)] - \tau\} \right\} \\
&= E \left\{ \frac{I(L \leq t_0)I(T_2 > t_0, T_2 < C)}{\alpha D(t_0, T_2)} \tilde{A}(t_0) \{I[\log(T_2 - t_0) \leq \tilde{A}^T(t_0)\beta_0(\tau, t_0)] - \tau\} \right\} \\
&= E \left\{ \frac{I(T_2 > t_0)\tilde{A}(t_0) \{I[\log(T_2 - t_0) \leq \tilde{A}^T(t_0)\beta_0(\tau, t_0)] - \tau\}}{\alpha D(t_0, T_2)} E[I(L \leq t_0, C > T_2) \mid T_1, T_2] \right\} \\
&= E \left\{ I(T_2 > t_0)\tilde{A}(t_0) \{I[\log(T_2 - t_0) \leq \tilde{A}^T(t_0)\beta_0(\tau, t_0)] - \tau\} \right\} = 0.
\end{aligned}$$

6.2 Proof of Theorem 1

The key step of the proof is to show that $\hat{D}(s, t)$ ($s < t$) is uniformly consistent under regularity conditions C1–C4. Specifically, define

$$\begin{aligned}
\xi_s(L_i^*, Y_i^*, \eta_i^*, t) &= \frac{I(L_i^* \leq s < Y_i^* \leq t, \eta_i^* = 0)}{C_s(Y_i^*)} - \int_s^t \frac{I(L_i^* \leq s < u \leq Y_i^*)}{C_s^2(u)} W_s(du), \\
R_{1n,s}(t) &= \int_s^t \frac{[C_s(u) - C_{n,s}(u)]^2}{C_{n,s}(u)C_s^2(u)} W_s(du), \\
R_{2n,s}(t) &= \int_s^t \left\{ \frac{1}{C_{n,s}(u)} - \frac{1}{C_s(u)} \right\} \left[W_{n,s}(du) - W_s(du) \right], \\
R_{n,s}(t) &= R_{1n,s}(t) + R_{2n,s}(t).
\end{aligned}$$

Then

$$\Lambda_n(t \mid s) - \Lambda(t \mid s) = \frac{1}{n} \sum_{i=1}^n \xi_s(L_i^*, Y_i^*, \eta_i^*, t) + R_{n,s}(t)$$

with $E[\xi_s(L_i^*, Y_i^*, \eta_i^*, t)] = 0$. We can show

$$\sup_{(s,t) \in \mathcal{S} \times \mathcal{T}} |R_{n,s}(t)| = o_p(n^{-1/2}),$$

where $\mathcal{S} \times \mathcal{T} = \{(s, t): s \in (a_L^*, b_Y^*], u \in (s, b_Y^*)\}$. This is because

$$|R_{1n,s}(t)| \leq \sup_{s < u \leq t} |C_s(u) - C_{n,s}(u)|^2 / \inf_{s < u \leq t} [C_{n,s}(u)C_s^2(u)].$$

By the LIL for empirical distribution functions and almost surely uniformly zero-away boundness of both $C_{n,s}(u)$ and $C_s^2(u)$ on $\mathcal{S} \times \mathcal{T}$, we have

$$\sup_{(s,t) \in \mathcal{S} \times \mathcal{T}} |R_{1n,s}(t)| = O(n^{-1} \log \log n), a.s.$$

Similarly, we can show $\sup_{(s,t) \in \mathcal{S} \times \mathcal{T}} |R_{2n,s}(t)| = O(n^{-1} \log \log n)$, *a.s.* and thus

$$\sup_{(s,t) \in \mathcal{S} \times \mathcal{T}} |R_{n,s}(t)| = o_p(n^{-1/2}).$$

By Taylor expansion, we have

$$\begin{aligned} \hat{S}(t | s) - S(t | s) &= \frac{1}{n} \sum_{i=1}^n \{ -S(t | s) \xi_s(L_i^*, Y_i^*, \eta_i^*, t) \} + o_p^{\mathcal{S} \times \mathcal{T}}(n^{-1/2}) \quad (7) \\ &\equiv \frac{1}{n} \sum_{i=1}^n l_i(s, t) + o_p^{\mathcal{S} \times \mathcal{T}}(n^{-1/2}), \end{aligned}$$

where $l_i(s, t) = -S(t | s) \xi_s(L_i^*, Y_i^*, \eta_i^*, t)$ and $El_i(s, t) = 0$.

By results in Gijbels and Wang (1993), we have

$$\hat{S}_{T_2}(s) - S_{T_2}(s) = \frac{1}{n} \sum_{i=1}^n a_i(s) + o_p^{[0, \tilde{b}]}(n^{-1/2}), \quad \tilde{b} < b_Y,$$

where

$$a_i(s) = -S_{T_2}(s) \left[\frac{I(L_i^* \leq Y_i^* \leq s, \eta_i^* = 1)}{\tilde{R}(Y_i^*)} - \int_0^s \frac{I(L_i^* \leq u \leq Y_i^*)}{\tilde{R}^2(u)} d\tilde{W}(u) \right],$$

$\tilde{W}(u) = P(L^* \leq Y^* \leq u, \eta^* = 1)$, $\tilde{R}(u) = P(L^* \leq u \leq Y^*)$ and $Ea_i(s) = 0$. Taylor expansion indicates

$$\begin{aligned} \frac{\hat{S}(t|s)}{\hat{S}_{T_2}(s)} - \frac{S(t|s)}{S_{T_2}(s)} &= \frac{1}{n} \sum_{i=1}^n \left[\frac{l_i(s, t)}{S_{T_2}(s)} - \frac{S(t|s)a_i(s)}{S_{T_2}^2(s)} \right] + o_p^{\mathcal{S} \times \mathcal{T}}(n^{-1/2}) \\ &\equiv \frac{1}{n} \sum_{i=1}^n k_i(t, s) + o_p^{\mathcal{S} \times \mathcal{T}}(n^{-1/2}) \end{aligned}$$

with $E\{k_i(s, t)\} = 0$. This, coupled with simple algebraic manipulation, implies that

$$\begin{aligned} \hat{D}(s, t) - D(s, t) &= \frac{1}{n} \sum_{i=1}^n \left[\left[I(L_i^* \leq s < Y_i^*) \frac{S(t|s)}{S_{T_2}(s)} - D(s, t) \right] + \frac{1}{n} \sum_{j=1}^n k_i(s, t) I(L_j^* \leq s < Y_j^*) \right] \\ &\quad + o_p^{\mathcal{S} \times \mathcal{T}}(n^{-1/2}) \\ &\equiv \frac{1}{n} \sum_{i=1}^n d_i(s, t) + o_p^{\mathcal{S} \times \mathcal{T}}(n^{-1/2}) \end{aligned} \tag{8}$$

with $E d_i(s, t) = 0$.

Next, we show $\{d_i(s, t), s \in \mathcal{S}, t \in \mathcal{T}\}$ is Donsker. We first note that $\{I_i(s, t), s \in \mathcal{S}, t \in \mathcal{T}\}$ forms a Donsker class. This is because the class of indicator functions is Donsker, $C_s(u)$ and $C_s(Y_i^*)$ are uniformly bounded away from 0 on $\mathcal{S} \times \mathcal{T}$ and the map $\pi: x(s, u) \rightarrow \int_s^t x(s, u) W_s(du)$ is a linear continuous map. Applying similar arguments, coupled with the boundness of $S_{T_2}^{-1}(s)$ on $\mathcal{S}$, shows that $\{d_i(s, t), s \in \mathcal{S}, t \in \mathcal{T}\}$ is Donsker.

Since the function class $\{d_i(s, t), s \in \mathcal{S}, t \in \mathcal{T}\}$ is Donsker and hence Glivenko-Cantelli, we have $\hat{D}(s, t)$ is uniformly consistent for $D(s, t)$ on $\mathcal{S} \times \mathcal{T}$. By the functional law of the iterated logarithm (Goodman et al., 1981), equation (8) implies $\sup_{(s, t) \in \mathcal{S} \times \mathcal{T}} |\hat{D}(s, t) - D(s, t)| = o(n^{-1/2+r})$ for $0 < r < \frac{1}{2}$ and consequently

$$\sup_{b, \tau, t_0} \|n^{-1/2} S_n(b, \tau, t_0) - n^{-1/2} S_n^D(b, \tau, t_0)\| = o(n^{-1/2+r}), \quad a.s. \tag{9}$$

Based on this result, the rest proof of Theorem 1 can be completed by following the same lines of Yang and Peng (2016).

6.3 Proof of Theorem 2

Let $\approx$ denote asymptotic equivalence uniformly in $\tau \in [\tau_L, \tau_U]$ and $t_0 \in [t_L, t_U]$. Simple algebraic manipulations show that

$$\begin{aligned}
 & S_n\{\beta_0(\tau, t_0), \tau, t_0\} \\
 &= S_n^D\{\beta_0(\tau, t_0), \tau, t_0\} + [S_n\{\beta_0(\tau, t_0), \tau, t_0\} - S_n^D\{\beta_0(\tau, t_0), \tau, t_0\}] \\
 &\approx n^{-1/2} \sum_{i=1}^n \xi_{1,i}(\tau, t_0) - n^{-1/2} \sum_{i=1}^n A_i^*(t_0) \frac{n^{-1} \sum_{j=1}^n d_j(t_0, Y_i^*)}{D^2(t_0, Y_i^*)} I(L_i^* \leq t_0) I(Y_i^* > t_0) \eta_i^* \times \{I[\log(Y_i^* - t_0)] \\
 &\leq A_i^{*T}(t_0) \beta_0(\tau, t_0) - \tau\} \\
 &= n^{-1/2} \sum_{i=1}^n \xi_{1,i}(\tau, t_0) - n^{-1/2} \sum_{i=1}^n \left\{ \sum_{j=1}^n \frac{A_j^*(t_0) I(L_j^* \leq t_0) I(Y_j^* > t_0) \eta_j^* \{I[\log(Y_j^* - t_0)] \leq A_j^{*T}(t_0) \beta_0(\tau, t_0) - \tau\}}{n D^2(t_0, Y_j^*)} d_i(t_0, Y_j^*) \right\} \\
 &\approx n^{-1/2} \sum_{i=1}^n \{\xi_{1,i}(\tau, t_0) - \xi_{2,i}(\tau, t_0)\}.
 \end{aligned}$$

where

$$\begin{aligned}
 \xi_{1,i}(\tau, t_0) &= I(L_i^* \leq t_0) I(Y_i^* > t_0) \eta_i^* A_i^*(t_0) \{I[\log(Y_i^* - t_0)] \leq A_i^{*T}(t_0) \beta_0(\tau, t_0) - \tau\} D(t_0, Y_i^*)^{-1} \text{ and} \\
 \xi_{2,i}(\tau, t_0) &= E_{\omega_j^*}[\xi_{1,j}(\tau, t_0) D(t_0, Y_j^*)^{-1} d_i(t_0, Y_j^*)] \text{ with } \omega_i^* \text{ denoting } (X_i^*, Y_i^*, \delta_i^*, \eta_i^*, L_i^*) \text{ and } E_{\omega_j^*}
 \end{aligned}$$

representing the expectation over $\omega_j^*, j = 1, \dots, n$. We can show that $\{\xi_{1,i}(\tau, t_0) - \xi_{2,i}(\tau, t_0), \tau \in [\tau_L, \tau_U], t_0 \in [t_L, t_U]\}$ is Donsker and thus $S_n\{\beta_0(\tau, t_0), \tau, t_0\}$ converges weakly to a mean zero Gaussian process with covariance matrix $\Sigma(\tau', t'_0, \tau, t_0) = E\{\xi_1(\tau', t'_0) \xi_1(\tau, t_0)^T\}$, where $\xi(\tau, t_0) = \xi_{1,i}(\tau, t_0) - \xi_{2,i}(\tau, t_0)$.

Following the similar line of Yang and Peng (2016), we can show that $n^{1/2}\{\hat{\beta}(\tau, t_0) - \beta_0(\tau, t_0)\}$ converges weakly to a mean zero Gaussian process with covariance matrix

$$H\{\beta_0(\tau', t'_0), t'_0\}^{-1} E\{\xi_1(\tau', t'_0) \xi_1(\tau, t_0)^T\} H\{\beta_0(\tau, t_0), t_0\}^{-T}.$$

This completes the proof of Theorem 2.

6.4 A sample-based estimate for the asymptotic covariance matrix of

$$\sqrt{n}\{\hat{\beta}(\tau, t_0) - \beta_0(\tau, t_0)\}$$

We can similarly derive a closed-form sample-based covariance estimate by following the four-step procedure presented in Yang and Peng (2016). The detailed procedure follows.

1. Calculate $\hat{\Sigma}(\tau, t_0, \tau, t_0) = n^{-1} \sum_{i=1}^n \hat{\xi}_i(\tau, t_0)^{\otimes 2}$, where

$$\begin{aligned} \hat{\xi}_i(\tau, t_0) &= \frac{I(L_i^* \leq t_0, Y_i^* > t_0) \eta_i^*}{\hat{D}(t_0, Y_i^*)} A_i^*(t_0) \{I[\log(Y_i^* - t_0) \leq A_i^{*T}(t_0) \hat{\beta}(\tau, t_0)] - \tau\} \\ &- \sum_{j=1}^n \frac{I(L_j^* \leq t_0, Y_j^* > t_0) \eta_j^* A_j^*(t_0) \{I[\log(Y_j^* - t_0) \leq A_j^{*T}(t_0) \hat{\beta}(\tau, t_0)] - \tau\}}{n \hat{D}^2(t_0, Y_j^*)} \times \hat{d}_i(t_0, Y_j^*) \end{aligned}$$

Here,

$$\begin{aligned} \hat{d}_i(t_0, Y_j^*) &= I(L_i^* \leq t_0 < Y_i^*) \frac{\hat{S}(Y_j^* | t_0)}{\hat{S}_{T_2}(t_0)} - \hat{D}(t_0, Y_j^*) + \frac{1}{n} \sum_{p=1}^n \hat{k}_i(t_0, Y_j^*) I(L_p^* \leq t_0 < Y_p^*) \\ \hat{k}_i(t_0, Y_j^*) &= \frac{\hat{l}_i(t_0, Y_j^*)}{\hat{S}_{T_2}(t_0)} - \frac{\hat{S}(Y_j^* | t_0) \hat{a}_i(t_0)}{\hat{S}_{T_2}^2(t_0)} \\ \hat{l}_i(t_0, Y_j^*) &= -\hat{S}(Y_j^* | t_0) \left\{ \frac{I(L_i^* \leq t_0 < Y_i^* \leq Y_j^*, \eta_i^* = 0)}{C_{n, t_0}(Y_i^*)} \right. \\ &- \left. \sum_{m: t_0 < Y_m^* \leq Y_j^*} \frac{I(L_i^* \leq t_0 < Y_m^* \leq Y_i^*)}{nC_{n, t_0}^2(Y_m^*)} I(L_m^* \leq t_0 < Y_m^*, \eta_m^* = 0) \right\} \\ \hat{a}_i(t_0) &= -\hat{S}_{T_2}(t_0) \left\{ \frac{I(L_i^* \leq Y_i^* \leq t_0, \eta_i^* = 1)}{\tilde{R}_n(Y_i^*)} - \sum_{m: Y_m^* \leq t_0} \frac{I(L_i^* \leq Y_m^* \leq Y_i^*)}{n \tilde{R}_n^2(Y_m^*)} I(L_m^* \leq Y_m^*, \eta_m^* = 1) \right\} \end{aligned}$$

$$\text{with } \tilde{R}_n(u) = \frac{1}{n} \sum_{k=1}^n (L_k^* \leq u \leq Y_k^*).$$

2. Use spectral decomposition to find a symmetric matrix $E_n(\tau, t_0)$ such that $\hat{\Sigma}(\tau, t_0, \tau, t_0) = E_n^2(\tau, t_0)$.
3. Calculate $D_n(\tau, t_0) = [S_n^{-1}\{e_{n,1}(\tau, t_0), \tau, t_0\} - \hat{\beta}(\tau, t_0), S_n^{-1}\{e_{n,2}(\tau, t_0), \tau, t_0\} - \hat{\beta}(\tau, t_0)]$ where $e_{n,j}$ is the j th column of $E_n(\tau, t_0)$, and $S_n^{-1}\{e, \tau, t_0\}$ is defined as the solution to $S_n(b, \tau, t_0) - e = 0$.
4. Estimate the asymptotic covariance matrix of $\sqrt{n}\{\hat{\beta}(\tau, t_0) - \beta_0(\tau, t_0)\}$ by

$$n\mathbf{D}_n(\tau', t'_0)\mathbf{E}_n^{-1}(\tau', t'_0)\widehat{\boldsymbol{\Sigma}}(\tau', t'_0, \tau, t_0)\mathbf{E}_n^{-1}(\tau, t_0)\mathbf{D}_n^T(\tau, t_0).$$

In the special case that $\tau' = \tau$ and $t'_0 = t_0$, the estimate for the asymptotic variance matrix is simplified as $n\{\mathbf{D}_n^{\otimes 2}(\tau, t_0)\}$.

Fig. 1. Summary of simulation results under Scenario 1: EmpBias of the YP estimator; EmpBias, EmpSE, EstSE and empirical coverage rate for the proposed estimator of $LCQRR(\tau; t_0)$.

Fig. 2. Summary of simulation results under Scenario 2: EmpBias of the YP estimator; EmpBias, EmpSE, EstSE and empirical coverage rate for the proposed estimator of $LCQRR(\tau; t_0)$.

Table 1

Summary of simulation setups with $p_1 = P(Y < L)$, $p_2 = P(\delta^* = 0)$, $p_3 = P(\eta^* = 0)$ and $p_4 = P(\delta^* = 0, \eta^* = 1)$.

θ	p	L_0	D_0	p_1	p_2	p_3	p_4
Scenario 1: $T_1 \sim \text{Weibull}(2, 0.5)$, $T_2 \sim \text{Weibull}(3; 2, 0.35)$							
1	0.86	$\text{Unif}(0, 1.9)$	$\text{Beta}(1.4, 1) \times (1.95 - 0.8L)^2$	0.30	0.47	0.24	0.35
2	0.86	$\text{Unif}(0, 1.9)$	$\text{Beta}(1.4, 1) \times (1.95 - 0.8L)^2$	0.30	0.54	0.24	0.36
3	0.86	$\text{Unif}(0, 1.9)$	$\text{Beta}(1.4, 1) \times (1.95 - 0.8L)^2$	0.30	0.57	0.24	0.38
Scenario 2: $T_1 \sim \text{Weibull}(2.5, 0.75)$, $T_2 \sim \text{Weibull}(3, 0.4)$							
1	0.89	$\min\text{Weibull}(1.4, 0.52), 1.9g$	$\text{Beta}(1.3, 1) \times (2 - 0.8L)^2$	0.45	0.33	0.24	0.24
2	0.89	$\min\text{Weibull}(1.2, 0.54), 1.9g$	$\text{Beta}(1.4, 1) \times (2.2 - 1.1L)^2$	0.45	0.32	0.24	0.20
3	0.89	$\min\text{Weibull}(1.0, 0.55), 1.9g$	$\text{Beta}(1.6, 1) \times (2.2 - 1.2L)^2$	0.45	0.28	0.24	0.17

Table 2

Summary of simulation study: EmpBias, EmpSE and EstSE of $\hat{\Delta}_\tau$ as well as empirical rejection rates for H_{01} and H_{02} .

θ	τ	EmpBias	EmpSE	EstSE	H_{01} EmpRR	H_{02} EmpRR
$\hat{\Delta}_\tau$						
Scenario 1						
$t_0 \in [0.65, 1.30]$						
1	0.25	0.000	0.143	0.148	0.048	0.050
	0.50	0.001	0.125	0.125	0.052	0.047
	0.75	-0.002	0.113	0.114	0.055	0.045
2	0.25	-0.001	0.133	0.134	1.000	0.090
	0.50	-0.003	0.111	0.112	0.999	0.125
	0.75	-0.001	0.103	0.106	0.989	0.142
3	0.25	0.000	0.118	0.122	1.000	0.112
	0.50	0.000	0.102	0.106	1.000	0.171
	0.75	-0.00	0.103	0.103	1.000	0.202
Scenario 2						
$t_0 \in [0.62, 1.20]$						
1	0.25	0.000	0.150	0.153	0.051	0.053
	0.50	0.001	0.124	0.124	0.048	0.056
	0.75	-0.002	0.108	0.109	0.045	0.056
2	0.25	0.001	0.125	0.127	1.000	0.124
	0.50	0.001	0.098	0.102	1.000	0.163
	0.75	-0.004	0.087	0.093	0.999	0.167
3	0.25	0.001	0.107	0.108	1.000	0.162
	0.50	-0.003	0.087	0.091	1.000	0.173
	0.75	-0.000	0.103	0.103	1.000	0.202

Table 3

Summary of simulation study: EmpBias, EmpSE and EstSE of $\hat{\mathcal{L}}_{\tau_0}$ over $\tau \in [0.15, 0.85]$ as well as empirical rejection rates for H_{03} and H_{04} .

θ	t_0	$\hat{\mathcal{L}}_{t_0}$						H_{04} EmpRR
		EmpBias	EmpSE	EstSE	H_{03} EmpRR	H_{04} EmpRR		
Scenario 1								
1	0.7	0.004	0.139	0.145	0.045	0.045		0.045
	1.0	0.002	0.150	0.149	0.055	0.045		0.045
	1.2	0.002	0.179	0.175	0.055	0.046		0.046
2	0.7	0.003	0.154	0.155	0.901	0.072		0.072
	1.0	-0.002	0.155	0.153	0.979	0.118		0.118
	1.2	0.003	0.174	0.174	0.976	0.124		0.124
3	0.7	0.003	0.154	0.157	1.000	0.124		0.124
	1.0	0.000	0.159	0.160	1.000	0.257		0.257
	1.2	0.001	0.178	0.183	1.000	0.175		0.175
Scenario 2								
1	0.7	-0.002	0.142	0.145	0.048	0.054		0.054
	0.9	-0.003	0.145	0.143	0.048	0.046		0.046
	1.1	0.001	0.173	0.170	0.058	0.052		0.052
2	0.7	0.001	0.143	0.142	0.965	0.083		0.083
	0.9	-0.001	0.132	0.135	0.995	0.167		0.167
	1.1	-0.004	0.143	0.146	0.998	0.237		0.237
3	0.7	0.002	0.140	0.142	1.000	0.186		0.186
	0.9	-0.003	0.129	0.131	1.000	0.386		0.386
	1.1	0.003	0.142	0.138	1.000	0.515		0.515

Table 4

Denmark Diabetes Registry Study: estimated $LCQRR(\tau, t_0)$ by the proposed method and the YP approach, 95% pointwise Wald-type bootstrapping confidence interval and corresponding p-value.

t_0	Proposed method			YP approach		
	$LCQRR(\tau, t_0)$	95% CI	P-value	$LCQRR(\tau, t_0)$	95% CI	P-value
$\tau = 0.25$						
12	1.95	(1.40, 2.50)	<0.001	2.08	(1.53, 2.62)	<0.001
15	1.87	(1.23, 2.52)	<0.001	1.95	(1.27, 2.62)	<0.001
18	1.87	(1.41, 2.34)	<0.001	1.54	(1.05, 2.03)	<0.001
21	1.30	(0.78, 1.82)	<0.001	1.10	(0.37, 1.83)	0.003
25	0.98	(0.21, 1.76)	0.013	0.69	(-0.66, 2.04)	0.31
27	0.85	(-0.32, 2.01)	0.15	0.47	(-0.97, 1.91)	0.52
$\tau = 0.5$						
12	1.75	(1.20, 2.50)	<0.001	1.87	(1.35, 2.40)	<0.001
15	1.44	(1.10, 1.77)	<0.001	1.61	(1.22, 2.00)	<0.001
18	1.48	(0.89, 2.08)	<0.001	1.53	(0.75, 2.31)	<0.001
21	1.15	(0.37, 1.93)	0.004	0.29	(-0.87, 1.44)	0.62
25	0.76	(-0.36, 1.89)	0.18	0.06	(-1.02, 1.14)	0.91
27	0.44	(-0.73, 1.62)	0.46	0.07	(-0.85, 0.99)	0.88

Table 5

Denmark Diabetes Registry Study: estimates for the change rate of $LCQRR(\tau; t_0)$ by diabetes onset age, 95% pointwise Wald-type bootstrapping confidence intervals, and corresponding p-values.

t_0	change rate of $LCQRR(\tau; t_0)$	95% CI	P-value
$\tau = 0.25$			
12	-0.04	(-0.19, 0.10)	0.55
15	-0.07	(-0.24, 0.10)	0.41
18	-0.01	(-0.14, 0.11)	0.84
21	-0.02	(-0.27, 0.23)	0.89
25	0.12	(-0.25, 0.48)	0.54
27	0.18	(-0.28, 0.64)	0.43
$\tau = 0.5$			
12	0.05	(-0.07, 0.17)	0.42
15	-0.05	(-0.18, 0.08)	0.43
18	0.03	(-0.16, 0.22)	0.77
21	0.14	(-0.10, 0.38)	0.24
25	0.24	(-0.12, 0.59)	0.19
27	0.19	(-0.23, 0.62)	0.39