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Quantile Regression for Survival Data

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Abstract

Quantile regression offers a useful alternative strategy for analyzing survival data. Compared with traditional survival analysis methods, quantile regression allows for comprehensive and flexible evaluations of covariate effects on a survival outcome of interest while providing simple physical interpretations on the time scale. Moreover, many quantile regression methods enjoy easy and stable computation. These appealing features make quantile regression a valuable practical tool for delivering in-depth analyses of survival data. This article provides a review of a comprehensive set of statistical methods for performing quantile regression with different types of survival data. The review covers various survival scenarios, including randomly censored data, data subject to left truncation or censoring, competing risks and semicompeting risks data, and recurrent events data. Two real-world examples are presented to illustrate the utility of quantile regression for practical survival data analyses.

1. BACKGROUND AND MOTIVATION

The problem of analyzing survival (or time-to-event) data arises in a number of scientific fields. For example, an event time of interest can be survival time of a cancer patient recorded in a medical study, time to high school dropout studied by sociologists, survival time of a new business addressed in economic research, or lifetime of a part under stress evaluated in an engineering reliability study. A common feature of survival data is that they often contain incomplete time-to-event information due to censoring or truncation. Censoring occurs when an event time is known to have occurred only within certain intervals. Truncation is defined as a condition that excludes certain subjects from the study population. Statistical methods for analyzing survival data need to appropriately account for various forms of censoring and truncation.

To evaluate the association between a survival outcome and a set of explanatory variables (or covariates), the accelerated failure time (AFT) model has been extensively studied in the literature as a counterpart of linear regression in survival analysis (e.g., Miller 1976, Prentice 1978, Buckley & James 1979, Wei & Gail 1983, Ritov 1990, Tsiatis 1990, Wei et al. 1990). Consider an event time T and a $p \times 1$ covariate vector $\tilde{\boldsymbol{Z}}$. The AFT model regresses a survival response, $Y \doteq \log(T)$ or another monotone transformation of T, over $\tilde{\boldsymbol{Z}}$; that is,

$$Y = \boldsymbol{Z}^{\mathsf{T}}\tilde{\boldsymbol{b}} + \epsilon,$$

where $\tilde{\boldsymbol{b}}$ is a vector of unknown regression coefficients and ϵ is an error term with an unknown distribution independent of $\tilde{\boldsymbol{Z}}$. The assumption that ϵ is independent of $\tilde{\boldsymbol{Z}}$ confines covariates to affect only the location of the distribution of Y. However, this is often too restrictive in real applications. For example, an analysis of a dialysis data set presented in Section 5.1 suggests that the symptom severity of restless leg syndrome (RLS) may only impact the lower range and not the upper range of the survival function of dialysis patients. The AFT model, which assumes pure location shift effects, would fail to accommodate such an inhomogeneous effect of RLS.

An alternative regression strategy for survival data is to use the Cox proportional hazards (PH) model (Cox 1972, Andersen & Gill 1982) Specifically, the Cox PH model relates the conditional hazard function of T, $\lambda(t|\tilde{\boldsymbol{Z}}) \doteq \lim_{\Delta \to 0} \Delta^{-1} \Pr\{t \in (t, t+\Delta] | T \geq t, \tilde{\boldsymbol{Z}}\}$, to covariates in $\tilde{\boldsymbol{Z}}$ multiplicatively without specifying a parametric baseline hazard; that is,

$$\lambda(t|\boldsymbol{Z}) = \lambda_0(t) \exp\{\boldsymbol{Z}^{\mathsf{T}}\tilde{\boldsymbol{b}}\},$$

where $\lambda_0(t)$ is an unspecified baseline hazard function, and $\tilde{\boldsymbol{b}}$ is an unknown regression coefficient vector. The Cox PH model is widely used in the practice of survival analysis. Nevertheless, the Cox regression model requires covariate-specific hazards to be proportional. This key assumption essentially exerts a location shift model for a monotonically transformed survival function of T. This limits the applications of the Cox PH model in scenarios with inhomogeneous covariate effects as exemplified above. Under the Cox PH model, covariate effects are formulated on the conditional hazard function of T, which lacks a physical interpretation on event times (Reid 1994).

Quantile regression (Koenker & Bassett 1978) offers a natural remedy for accommodating heterogeneous covariate effects while retaining straightforward physical interpretations. A comprehensive review of quantile regression methodology was provided by Koenker (2017). Quantile regression has received increased attention in survival analysis because event times themselves are often of scientific interest, and quantiles are more flexible and robust quantitative tools for characterizing event times than mean-based devices. For example, in the presence of censoring with bounded support, mean survival time may not be identifiable, while quantiles may be identifiable.

For a survival time T, a standard quantile regression model assumes that the τth conditional quantile of $Y \doteq \log(T)$ given $\boldsymbol{Z} = (1, \tilde{\boldsymbol{Z}}^{\mathsf{T}})^{\mathsf{T}}$, defined as $Q_Y(\tau|\boldsymbol{Z}) \doteq \inf\{t : \Pr(Y \leq t|\boldsymbol{Z}) \geq \tau\}$, is

linearly related to covariates in $\boldsymbol{Z}$. That is,

$$Q_Y(\tau|\boldsymbol{Z}) = \boldsymbol{Z}^\top \boldsymbol{\beta}_0(\tau), \quad \tau \in [\tau_L, \tau_U], \qquad 1.$$

where $0 \le \tau_L \le \tau_U < 1$ and $\boldsymbol{\beta}_0(\tau)$ is a $(p+1) \times 1$ vector of unknown regression coefficients. A nonintercept coefficient in $\boldsymbol{\beta}_0(\tau)$ represents a covariate effect on the τth conditional quantile of $\log(T)$. By allowing $\boldsymbol{\beta}_0(\tau)$ to change with τ, quantile regression permits varying covariate effects on different segments of the response distribution. This feature confers the flexibility to accommodate inhomogeneous covariate effects.

When $\tau_L = \tau_U$, the model in Equation 1 is referred to as a locally linear quantile regression model because it only asserts local linearity between the conditional quantile of $\log(T)$ and $\boldsymbol{Z}$ at a single quantile level. When $\tau_L < \tau_U$, Equation 1 imposes a global linearity for the conditional quantile of $\log(T)$ throughout the τ interval $[\tau_L, \tau_U]$ and thus is referred to as a globally linear quantile regression model. A globally linear quantile regression model can provide a platform for investigating the dynamic pattern of covariate effects, while paying the price of imposing a stronger model assumption compared with a locally linear quantile regression model.

It is easy to see that the AFT model is a special case of the model in Equation 1 with $\boldsymbol{\beta}_0(\tau) = \{Q_\epsilon(\tau), \boldsymbol{b}^\top\}^\top$, where $Q_\epsilon(\tau)$ denotes the τth percentile of ϵ. Under the standard Cox PH model, $Q_{\log \Lambda_0(T)}(\tau|\boldsymbol{Z}) = \log\{-\log(1-\tau)\} + \tilde{\boldsymbol{Z}}^\top \boldsymbol{b}$, where $\Lambda_0(t) = \int_0^t \lambda_0(u)\mathrm{d}u$. Given $\Lambda_0(\cdot)$ is an unknown function, the quantile interpretation of the Cox PH model is vague. Moreover, many interesting forms of heterogeneous covariate effects are excluded by the restrictive forms of $Q_T(\tau|Z)$ designated by the AFT model and the Cox PH model. In contrast, quantile regression modeling offers straightforward physical interpretations as well as greater flexibility to accommodate heterogeneous associations between covariates and the survival response. This serves as the key motivation for considering quantile regression as an alternative approach to analyzing survival data.

In this article, we present a comprehensive methodological framework that has been developed to perform quantile regression with survival data. Due to space limitations, the review is rather selective but covers a wide range of survival scenarios. More specifically, Section 2 is focused on the standard survival setting with randomly censored data. Section 3 includes discussions of quantile regression methods applicable to more complex survival settings that involve left truncation or left censoring, competing risks, and semicompeting risks. Recent method developments for recurrent events data are presented in Section 4. Two real data examples are presented in Section 5 to illustrate the practical utility of quantile regression methods for survival analyses. Section 6 concludes the article with a brief summary and a few remarks.

2. QUANTILE REGRESSION FOR RANDOMLY CENSORED DATA

Let T denote time to event subject to right censoring by C, and let $Y = \log(T)$. Define $\tilde{T} = T \wedge C$ and $\Delta = I(T \le C)$, where $\wedge$ is the minimum operator. The observed data consist of n independent and identically distributed (i.i.d.) replicates of $(\tilde{T}, \Delta, \boldsymbol{Z})$, denoted by $(\tilde{T}_i, \Delta_i, \boldsymbol{Z}_i)$, $i = 1, \ldots, n$. Define $\tilde{Y} = \log(\tilde{T})$, $\tilde{Y}_i = \log(\tilde{T}_i)$, $U = \log(C)$, and $U_i = \log(C_i)$.

2.1. Random Right Censoring with *C* Always Known

In the absence of censoring, the regression quantile $\boldsymbol{\beta}_0(\tau)$ in Equation 1 is defined as the minimizer of the standard quantile loss function, $\sum_{i=1}^n \rho_\tau\{Y_i - (\boldsymbol{Z}_i^\top \boldsymbol{b}) \wedge U_i\}$, with respect to $\boldsymbol{b}$, where $\rho_\tau(x) = x\{\tau - I(x < 0)\}$ (Koenker & Bassett 1978).

When censoring is present and the censoring time C is fixed at prespecified values, by utilizing the fact that $Q_{\tilde{Y}}(\tau|\boldsymbol{Z}) = \{\boldsymbol{Z}^\top \boldsymbol{\beta}_0(\tau)\} \wedge U$, Powell (1984, 1986) proposed an adaptation of the

standard quantile loss function, which led to an estimator of $\boldsymbol{\beta}_0(\tau)$ given by $\arg\min_{\boldsymbol{b}} r(\boldsymbol{b},\tau)$, where

$$r(\boldsymbol{b},\tau)=\sum_{i=1}^{n}\rho_\tau\{\tilde{Y}_i-(\boldsymbol{Z}_i^{\mathsf{T}}\boldsymbol{b})\wedge U_i\}.$$

This estimation method is directly applicable to a more general case where C is always known but not necessarily fixed, and it is independent of T given $\boldsymbol{Z}$. Unlike the standard quantile loss function, $r(\boldsymbol{b},\tau)$ is not convex in $\boldsymbol{b}$ and thus it may have multiple local minima. Several authors, for example, Fitzenberger (1997), Buchinsky & Hahn (1998), and Chernozhukov & Hong (2001), contributed strategies to improve the numerical performance of Powell's estimator. An implementation of Powell's method is available in the `crq` function in the R package `quantreg` (Koenker et al. 2020).

2.2. Unconditionally Random Right Censoring

Censoring time C is not always observed in most survival settings. Under the assumption that T and C are independent and C is independent of $\boldsymbol{Z}$ (i.e., unconditionally random right censoring), Ying et al. (1995) proposed to estimate $\boldsymbol{\beta}_0(\tau)$ by solving the following estimating equation:

$$n^{-1/2}\sum_{i=1}^{n}\boldsymbol{Z}_i\left[\frac{I\{\tilde{Y}_i-\boldsymbol{Z}_i^{\mathsf{T}}\boldsymbol{\beta}(\tau)>0\}}{\widehat{G}\{\boldsymbol{Z}_i^{\mathsf{T}}\boldsymbol{\beta}(\tau)\}}-(1-\tau)\right]=0, \qquad 2.$$

where $\widehat{G}(\cdot)$ is the Kaplan–Meier estimate for $G(\cdot)$, which denotes the survival function of U. Since Equation 2 is not continuous and may not have an exact zero crossing, Ying et al. (1995) suggested obtaining the estimator of $\boldsymbol{\beta}_0(\tau)$ by minimizing the L_2 norm of the estimating function in Equation 2. The resulting objective function, however, may have multiple minima.

Employing the inverse probability of censoring weighting (IPCW) technique (Robins & Rotnitzky 1992), Zhou (2006) studied an alternative estimating equation for $\boldsymbol{\beta}_0(\tau)$, which is given by

$$n^{-1/2}\sum_{i=1}^{n}\boldsymbol{Z}_i\left[\frac{I\{\tilde{Y}_i\le\boldsymbol{Z}_i^{\mathsf{T}}\boldsymbol{\beta}(\tau),\Delta_i=1\}}{\widehat{G}(\tilde{Y}_i)}-\tau\right]=0. \qquad 3.$$

The estimating function in Equation 3 is monotone (Fygenson & Ritov 1994). Consequently, the solution to Equation 3 can be reformulated as the minimizer of a convex L_1-type convex function of $\boldsymbol{b}$,

$$\sum_{i=1}^{n}\left\{I(\Delta_i=1)\left|\frac{\tilde{Y}_i}{\widehat{G}(\tilde{Y}_i)}-\boldsymbol{b}^{\mathsf{T}}\frac{\boldsymbol{Z}_i}{\widehat{G}(\tilde{Y}_i)}\right|\right\}+\left|M^*-\boldsymbol{b}^{\mathsf{T}}\sum_{l=1}^{n}\left(-\frac{\boldsymbol{Z}_l I(\Delta_l=1)}{\widehat{G}(\tilde{Y}_l)}+2\boldsymbol{Z}_l\tau\right)\right|,$$

where M^* is an extremely large positive number selected to bound $\boldsymbol{b}^{\mathsf{T}}\sum_{l=1}^{n}(-\frac{\boldsymbol{Z}_l I(\Delta_l=1)}{\widehat{G}(\tilde{Y}_l)}+2\boldsymbol{Z}_l\tau)$ for all $\boldsymbol{b}$s in a compact parameter space. This minimization problem can be readily solved by the `l1fit` function in S-PLUS or the `rq` function in the R package `quantreg` (Koenker et al. 2020).

2.3. Conditionally Random Right Censoring

Conditionally random right censoring, which assumes C is independent of T given $\boldsymbol{Z}$, is the most commonly adopted random censoring mechanism. This censoring mechanism is less restrictive than those considered in Sections 2.1 and 2.2.

In this section, we first consider a globally linear quantile regression model,

$$Q_Y(\tau|\boldsymbol{Z})=\boldsymbol{Z}^{\mathsf{T}}\boldsymbol{\beta}_0(\tau),\quad \tau\in[0,\tau_U], \qquad 4.$$

and then discuss a locally linear quantile regression model with $\tau_L=\tau_U$.

2.3.1. Self-consistent approaches. By adapting the idea of redistributing censoring probability in the self-consistent Kaplan-Meier estimator (Efron 1967), Portnoy (2003) made the first attempt to estimate the globally linear quantile regression model in Equation 4 under the conditionally random right censoring assumption. The initial iterative self-consistent algorithm (Portnoy 2003) was simplified into a grid-based sequential estimation procedure (Neocleous et al. 2006), and the corresponding asymptotic study was conducted by Portnoy & Lin (2010).

The grid-based estimation procedure of Neocleous et al. (2006) is outlined as follows. First, define a grid of τ values, $\mathcal{G}_n$, as $0 = \tau_0 < \tau_1 < \cdots < \tau_{M_n} = \tau_U$. Let $\|\mathcal{G}_n\| = \max\{\tau_k - \tau_{k-1} : k = 1, \ldots, M_n\}$. Without further mentioning, $\mathcal{G}_n$ is adopted throughout Section 2.3. Assuming no censoring occurs below the τ_1th conditional quantile of T, one can obtain an estimate for $\boldsymbol{\beta}_0(\tau_1)$ from applying uncensored quantile regression. Next, one can estimate $\boldsymbol{\beta}_0(\tau_{k+1})$ sequentially for $k = 1, 2, \ldots, M_n$ by minimizing

$$\sum_{i \in K^c} \rho_{\tau_{k+1}}(\tilde{Y}_i - \boldsymbol{Z}_i^\top \boldsymbol{b}) + \sum_{i \in K} \left\{ w_{k+1,i} \cdot \rho_{\tau_{k+1}}(\tilde{Y}_i - \boldsymbol{Z}_i^\top \boldsymbol{b}) + (1 - w_{k+1,i}) \rho_{\tau_{k+1}}(Y^* - \boldsymbol{Z}_i^\top \boldsymbol{b}) \right\}, \qquad 5.$$

where Y^* is an extremely large value and K denotes the set of indices of censored observations that have been previously crossed (i.e., $C_i \le \boldsymbol{Z}_i^\top \hat{\boldsymbol{\beta}}(\tau)$). The weight $w_{k+1,i}$ takes the form $(\tau_{k+1} - \tau_l)/(1 - \tau_l)$ to approximate the conditional probability, $\Pr(C_i < T_i < \exp\{\boldsymbol{Z}_i \boldsymbol{\beta}_0(\tau_{k+1})\} | C_i < T_i, \boldsymbol{Z}_i)$, based on the estimates for $\boldsymbol{\beta}_0(\tau_1), \ldots, \boldsymbol{\beta}_0(\tau_k)$.

Peng (2012) proposed alternative formulations of the self-consistent approach based on stochastic integral equations. First, using a stochastic integral formulation and applying a stochastic integration by parts, Efron's (1967) self-consistent estimating equation for $F_Y(t)$ in the one-sample case can be reexpressed as

$$F_Y(t) = n^{-1} \sum_{i=1}^{n} \left[N_i(t) + R_i(t)\{1 - F_Y(t)\} \int_0^t \frac{R_i(u)}{\{1 - F_Y(u)\}^2} \mathrm{d}F_Y(u) \right],$$

where $N_i(t) = I(\tilde{Y}_i \le t, \Delta_i = 1)$, $R_i(t) = I(\tilde{Y}_i \le t,\ \Delta_i = 0)$, and $F_Y(t) = \Pr(Y \le t)$.

With t replaced by $\boldsymbol{Z}_i^\top \boldsymbol{\beta}(\tau)$, this equation evolves into an estimating equation for $\boldsymbol{\beta}_0(\tau)$:

$$n^{1/2} \boldsymbol{S}_n^{(\mathrm{SC})}(\boldsymbol{\beta}, \tau) \doteq n^{-1/2} \sum_{i=1}^{n} \boldsymbol{Z}_i \left[N_i\{\boldsymbol{Z}_i^\top \boldsymbol{\beta}(\tau)\} + R_i\{\boldsymbol{Z}_i^\top \boldsymbol{\beta}(\tau)\}(1 - \tau) \int_0^\tau \frac{R_i\{\boldsymbol{Z}_i^\top \boldsymbol{\beta}(u)\}}{(1 - u)^2} \mathrm{d}u - \tau \right] = 0. \quad 6.$$

Peng (2012) further justified several asymptotically equivalent variants of the estimating Equation 6, one of which takes the form of

$$n^{1/2} \boldsymbol{S}_n^{(\mathrm{MSC})}(\boldsymbol{\beta}, \tau) \doteq n^{-1/2} \sum_{i=1}^{n} \boldsymbol{Z}_i \left[N_i\{\boldsymbol{Z}_i^\top \boldsymbol{\beta}(\tau)\} + R_i\{\boldsymbol{Z}_i^\top \boldsymbol{\beta}(\tau)\} \frac{\tau - \psi_i(\boldsymbol{\beta}, \tau)}{1 - \psi_i(\boldsymbol{\beta}, \tau)} - \tau \right] = 0. \qquad 7.$$

Here, $\psi_i(\boldsymbol{\beta}, \tau) = \sup\{A_i(\boldsymbol{\beta}, \tau)\} \cdot I(A_i(\boldsymbol{\beta}, \tau) \text{ is not empty}) + \tau I(A_i(\boldsymbol{\beta}, \tau) \text{ is empty})$ with $A_i(\boldsymbol{\beta}, \tau) = \{u :\ 0 \le u < \tau,\ \boldsymbol{Z}_i^\top \boldsymbol{\beta}(u-) \le \tilde{Y}_i \le \boldsymbol{Z}_i^\top \boldsymbol{\beta}(u)\}$. The estimation procedure derived from Equation 7 is identical to the procedure of Neocleous et al. (2006) except for the estimation of $\boldsymbol{\beta}_0(\tau_1)$. That is, the procedure of Neocleous et al. (2006) estimates $\boldsymbol{\beta}_0(\tau_1)$ as the minimizer of Equation 5 with $w_{1,i} = 1$, whereas estimating $\boldsymbol{\beta}_0(\tau_1)$ based on Equation 7 is equivalent to minimizing Equation 5 with $w_{1,i} = 0$.

Large sample studies for the estimator $\widehat{\boldsymbol{\beta}}_{\mathrm{SC}}(\tau)$ obtained from solving Equation 6 are facilitated by the stochastic integral equation representation of $\boldsymbol{S}_n^{(\mathrm{SC})}(\boldsymbol{\beta}, \tau)$. Specifically, under certain regularity conditions and given $\lim_{n \to \infty} \|\mathcal{G}_n\| = 0$, $\sup_{\tau \in [\nu, \tau_U]} \|\widehat{\boldsymbol{\beta}}_{\mathrm{SC}}(\tau) - \boldsymbol{\beta}_0(\tau)\| \to_p 0$, where $0 < \nu < \tau_U$. If $n^{1/2} \lim_{n \to \infty} \|\mathcal{G}_n\| = 0$ is further satisfied, then $n^{1/2}\{\widehat{\boldsymbol{\beta}}_{\mathrm{SC}}(\tau) - \boldsymbol{\beta}_0(\tau)\}$ converges weakly to a Gaussian process for $\tau \in [\nu, \tau_U]$. The estimator defined based on Equation 7 is asymptotically equivalent to $\widehat{\boldsymbol{\beta}}_{\mathrm{SC}}(\cdot)$.

2.3.2. Martingale-based approach. Peng & Huang (2008) proposed to utilize the martingale structure underlying randomly censored data to construct an estimating equation for the model in Equation 4. Define $\Lambda_Y(t|\boldsymbol{Z}) = -\log\{1 - \Pr(Y \le t|\boldsymbol{Z})\}$, $N(t) = I(\tilde{Y} \le t, \Delta = 1)$, and $M(t) = N(t) - \Lambda_Y(t \wedge Y|\boldsymbol{Z})$. Let $N_i(t)$ and $M_i(t)$ be sample analogs of $N(t)$ and $M(t)$, respectively, and $i = 1, \ldots, n$. Note that $M_i(t)$ is the martingale process associated with the counting process $N_i(t)$. Thus, $E\{M_i(t)|\boldsymbol{Z}_i\} = 0$ for all $t > 0$, and $E\{\sum_{i=1}^n \boldsymbol{Z}_i[N_i\{\boldsymbol{Z}_i^\top \boldsymbol{\beta}_0(\tau)\} - \Lambda_Y\{\boldsymbol{Z}_i^\top \boldsymbol{\beta}_0(\tau) \wedge \tilde{Y}_i|\boldsymbol{Z}_i\}]\} = 0$ for $\tau[0, \tau_U]$. Since $\boldsymbol{Z}_i^\top \boldsymbol{\beta}_0(\tau)$ is monotone in $\tau \in [0, \tau_U]$, we have $\Lambda_Y\{\boldsymbol{Z}_i^\top \boldsymbol{\beta}_0(\tau) \wedge \tilde{Y}_i|\boldsymbol{Z}_i\} = \int_0^\tau I\{\tilde{Y}_i \ge \boldsymbol{Z}_i^\top \boldsymbol{\beta}_0(u)\}\mathrm{d}H(u)$, where $H(x) = -\log(1 - x)$. These findings suggest a stochastic integral–based estimating equation,

$$n^{1/2}\boldsymbol{S}_n^{(\mathrm{PH})}(\boldsymbol{\beta}, \tau) \doteq n^{-1/2}\sum_{i=1}^n \boldsymbol{Z}_i\left[N_i\{\boldsymbol{Z}_i^\top \boldsymbol{\beta}(\tau)\} - \int_0^\tau I\{\tilde{Y}_i \ge \boldsymbol{Z}_i^\top \boldsymbol{\beta}(u)\}\mathrm{d}H(u)\right] = 0. \quad 8.$$

An estimator of $\boldsymbol{\beta}_0(\tau)$, denoted by $\widehat{\boldsymbol{\beta}}_{\mathrm{PH}}(\tau)$, can be obtained through approximating the stochastic solution to Equation 8. Specifically, let $\widehat{\boldsymbol{\beta}}_{\mathrm{PH}}(\tau)$ be a cadlag (i.e., right continuous with finite left limits) step function of τ that jumps only at the grid points of $\mathcal{G}_n$. The procedure to obtain $\widehat{\boldsymbol{\beta}}_{\mathrm{PH}}(\tau)$ follows.

1. Set $\exp\{\boldsymbol{Z}_i^\top \widehat{\boldsymbol{\beta}}_{\mathrm{PH}}(\tau_0)\} = 0$ for all i. Set $k = 0$.
2. Given $\exp\{\boldsymbol{Z}_i^\top \widehat{\boldsymbol{\beta}}_{\mathrm{PH}}(\tau_l)\}$ for $l \le k$, obtain $\widehat{\boldsymbol{\beta}}_{\mathrm{PH}}(\tau_{k+1})$ as the minimizer of the following L_1-type convex objective function:

$$l_{k+1}(\boldsymbol{b}) = \sum_{i=1}^n \left|\Delta_i \tilde{Y}_i - \Delta_i \boldsymbol{Z}_i^\top \boldsymbol{b}\right| + \left|Y^* - \sum_{l=1}^n (-\Delta_l \boldsymbol{Z}_l^\top \boldsymbol{b})\right| + \left|Y^* - \sum_{r=1}^n \left[(2\boldsymbol{Z}_r^\top \boldsymbol{b}) \sum_{l=0}^k I\{\tilde{Y}_r \ge \boldsymbol{Z}_r^\top \widehat{\boldsymbol{\beta}}_{\mathrm{PH}}(\tau_l)\}\{H(\tau_{l+1}) - H(\tau_l)\}\right]\right|,$$

   where Y^* is an extremely large value.
3. Replace k by $k + 1$ and repeat step 2 until $k = M_n$ or no feasible solution can be found for minimizing $l_k(\boldsymbol{b})$.

Peng & Huang (2008) established the uniform consistency and weak convergence of $\widehat{\boldsymbol{\beta}}_{\mathrm{PH}}(\cdot)$. Moreover, Peng (2012) showed that $\widehat{\boldsymbol{\beta}}_{\mathrm{PH}}(\cdot)$ is asymptotically equivalent to the self-consistent estimator $\widehat{\boldsymbol{\beta}}_{\mathrm{SC}}(\cdot)$ in that $\sup_{\tau \in [\nu, \tau_U]} \|n^{1/2}\{\widehat{\boldsymbol{\beta}}_{\mathrm{PH}}(\tau) - \widehat{\boldsymbol{\beta}}_{\mathrm{SC}}(\tau)\}\| = o_p(1)$ with $0 < \nu < \tau_U$. This theoretical result is consistent with the numerical results reported by Koenker (2008) and Peng (2012).

The `crq` function in the R package `quantreg` (Koenker et al. 2020) provides an implementation of $\widehat{\boldsymbol{\beta}}_{\mathrm{PH}}(\tau)$ based on an algorithm slightly different from the one presented above. An asymptotically equivalent grid-free estimation procedure for the model in Equation 4 was developed by Huang (2010).

2.3.3. Data augmentation approach. Yang et al. (2018) employed a variation of the data augmentation algorithm to tackle the estimation of the model in Equation 4 with $\tau_U = 1$. The basic idea is to apply the general principle of data augmentation (Tanner & Wong 1987) and employ an alternating process between imputation of censored values from the quantile functions and refitting of the quantile model using the imputed values. More specifically, the algorithm starts with a set of initial values, $\hat{\boldsymbol{\beta}}^{(0)}(\tau_k)$ $(k = 1, \ldots, M_n)$, obtained by parallel quantile regression estimators or existing quantile regression estimators. For $b = 1, \ldots, H$, draw $Y_i^{(b)}$ from the quantile process approximated by $\boldsymbol{Z}_i^\top \hat{\boldsymbol{\beta}}^{(b-1)}(\tau_k)$ conditional on the set of possible values for Y_i. Then, based on a pairwise bootstrapping sample of size n from $\{\boldsymbol{Z}_i, Y_i^{(b)}\}_{i=1}^n$, obtain updated estimates $\hat{\boldsymbol{\beta}}^{(b)}(\tau_k)$

via standard uncensored quantile regression. Lastly, take the final estimates as $\hat{\boldsymbol{\beta}}(\tau) = H^{-1}\sum_{b=1}^{H}\hat{\boldsymbol{\beta}}^{(b)}(\tau)$.

An appealing feature of Yang et al.'s (2018) approach is that it can handle different forms of censoring, including random censoring, double censoring, and interval censoring. As demonstrated by Monte Carlo simulations, the resulting estimator can achieve significant efficiency gains over the existing methods. The algorithm of Yang et al. (2018) is implemented by the R function `DArq`.

2.3.4. Adjusted loss function methods. Assume a locally linear quantile regression model, which is the model in Equation 1 with $\tau_L = \tau_U$ equal to a prespecified τ, i.e.,

$$Q_Y(\tau|\boldsymbol{Z}) = \boldsymbol{Z}^\top\boldsymbol{\beta}_0(\tau). \quad 9.$$

To account for random censoring in the estimation of the model in Equation 9, Wang & Wang (2009) proposed to modify the standard quantile loss function by twisting the idea of the self-consistent Kaplan-Meier estimator (Efron 1967). That is, one may redistribute the probability mass associated with each censored case, $\Pr(T_i > C_i|C_i, \boldsymbol{Z}_i)$, to the right through a local weighting scheme by $w_i(F_0)$, where

$$w_i(F_0) = \begin{cases} 1 & \Delta_i = 1 \text{ or } F_0(C_i|\boldsymbol{Z}_i) > \tau \\ \frac{\tau - F_0(C_i|\boldsymbol{Z}_i)}{1 - F_0(C_i|\boldsymbol{Z}_i)} & \Delta_i = 0 \text{ and } F_0(C_i|\boldsymbol{Z}_i) < \tau, \end{cases}$$

with $F_0(t|\boldsymbol{z}) = \Pr(T > t|\boldsymbol{Z} = \boldsymbol{z})$. Suppose $F_0(t|\boldsymbol{z})$ is known. An estimator of $\boldsymbol{\beta}_0(\tau)$ in Equation 9 can be obtained by minimizing the following objective function of $\boldsymbol{\beta}$:

$$n^{-1}\sum_{i=1}^{n}\Big[w_i(F_0)\rho_\tau(\tilde{Y}_i - \boldsymbol{Z}_i^\top\boldsymbol{\beta}) + \{1 - w_i(F_0)\}\rho_\tau(Y^* - \boldsymbol{Z}_i^\top\boldsymbol{\beta})\Big]. \quad 10.$$

In practice, $F_0(t|\boldsymbol{z})$ is usually unknown. In this case, Wang & Wang (2009) proposed to minimize the objective function Equation 10 with $F_0(\cdot)$ replaced by $\hat{F}(\cdot)$, the local Kaplan–Meier estimator—namely,

$$\hat{F}(t|\boldsymbol{z}) = 1 - \prod_{j=1}^{n}\left\{1 - \frac{B_{nj}(\boldsymbol{z})}{\sum_{k=1}^{n} I(\tilde{Y}_k \geq \tilde{Y}_j)B_{nk}(\boldsymbol{z})}\right\}^{N_j(t)}.$$

Here $B_{nk}(\boldsymbol{z})$ is a sequence of nonnegative weights adding up to 1, for example, the Nadaraya–Watson type weight, $B_{nk}(\boldsymbol{z}) = K(\frac{\boldsymbol{z}-\boldsymbol{z}_k}{b_n})/\sum_{i=1}^{n}K(\frac{\boldsymbol{z}-\boldsymbol{z}_i}{b_n})$, where $K(\cdot)$ is a density kernel function and b_n is a positive bandwidth converging to 0 as $n \to \infty$. The resulting estimator is shown to be consistent and asymptotically normal with root n rate under regularity conditions.

De Backer et al. (2019, 2020) investigated different strategies for adjusting the standard quantile loss function in order to accommodate randomly censored data. More specifically, letting $G_U(u|\boldsymbol{Z}) = \Pr(U > u|\boldsymbol{Z})$, De Backer et al. (2019) noted that the derivative of $\phi_\tau(a; Y, G_U(\cdot|\boldsymbol{Z})) \doteq (Y - a)\{\tau - I(Y \leq a)\} - (1 - \tau)\int_0^a\{1 - G_U(s|\boldsymbol{Z})\}ds$ with respect to a equals $-\{I(Y > a) - G_U(a|\boldsymbol{Z})(1 - \tau)\}$, which, conditional on $\boldsymbol{Z}$, has expectation zero with $a = \boldsymbol{Z}^\top\boldsymbol{\beta}_0(\tau)$ under the model in Equation 9. This key fact leads to an adjusted loss function for censored quantile regression,

$$\sum_{i=1}^{n}\phi_\tau(\boldsymbol{Z}_i^\top\boldsymbol{\beta}; Y_i, \hat{G}_U(\cdot|\boldsymbol{Z}_i)), \quad 11.$$

where $\hat{G}_U(\cdot|\boldsymbol{z})$ is a consistent estimator of $G_U(\cdot|\boldsymbol{z})$. When C is independent of $\boldsymbol{Z}$, $\hat{G}_U(\cdot|\boldsymbol{z})$ can be obtained through the Kaplan–Meier estimator of the survival distribution of C. Without assuming

the independence between C and $\boldsymbol{Z}$, $\hat{G}_U(\cdot|\boldsymbol{z})$ can be obtained through semiparametric modeling of C given $\boldsymbol{Z}$, or by directly using Beran's conditional Kaplan–Meier estimator (Beran 1981). De Backer et al. (2019) developed a numerically robust majorize-maximization algorithm to solve the minimization of the nonconvex adjusted loss function, Equation 11. Following a different view, De Backer et al. (2020) proposed to estimate the model in Equation 9 based on a minimum distance loss function, given by $\sum_{i=1}^{n}\{1-\hat{F}(\boldsymbol{Z}_i^{\top}\boldsymbol{\beta}(\tau)|\boldsymbol{Z}_i)-\tau\}^2$. De Backer et al. (2020) further suggested using a smooth double kernel version of $\hat{F}(\cdot|\boldsymbol{Z}_i)$. They also discussed how to handle high-dimensional covariates by employing the effective dimension reduction technique (Li et al. 1999, Xia et al. 2010). Desirable asymptotic properties, consistency and asymptotic normality, were established for these estimators of $\boldsymbol{\beta}_0(\tau)$ in Equation 9.

2.4. Inference Procedures

Inferences are important in practice. In the following, we discuss variance estimation and second-stage inference to help understand varying covariate effects on the survival outcome under quantile regression.

2.4.1. Variance estimation. Bootstrapping procedures have been justified and commonly used to make inferences under quantile regression with either uncensored response or censored survival response. For example, to estimate the asymptotic variance of the estimators discussed in Sections 2.1–2.3, one may use resampling methods that follow the idea of Parzen & Ying (1994) or apply the standard bootstrapping procedures that use resampling with replacement (Koenker 2005, Peng & Huang 2008).

Alternative methods without involving resampling have been developed for variance estimation under quantile regression. A main challenge is how to estimate the unknown densities involved in the formulas for asymptotic variances. Under random right censoring with known censoring time or unconditionally random censoring, Huang's (2002) technique can be directly applied to avoid smoothing-based density estimation, which may be unstable with small or moderate sample sizes. Specifically, let $\widehat{\boldsymbol{\beta}}(\tau)$ denote an estimator of $\boldsymbol{\beta}_0(\tau)$, and $\boldsymbol{S}_n\{\boldsymbol{\beta}(\tau),\tau\}$ denote the estimating function associated with $\widehat{\boldsymbol{\beta}}(\tau)$, for example, the left-hand side of Equations 2 and 3. Generally it can be shown that $\boldsymbol{S}_n\{\boldsymbol{\beta}_0(\tau),\tau\}$ converges to a mean-zero multivariate normal distribution with covariance matrix $\boldsymbol{\Sigma}(\tau)$, which may be consistently estimated by $\widehat{\boldsymbol{\Sigma}}(\tau)$. The following are the main steps to obtain a sample-based variance estimator:

1. Find a symmetric and nonsingular $(p+1)\times(p+1)$ matrix $\boldsymbol{E}_n(\tau)\doteq\{\boldsymbol{e}_{n,1}(\tau),\ldots,\boldsymbol{e}_{n,p+1}(\tau)\}$ such that $\widehat{\boldsymbol{\Sigma}}(\tau)=\{\boldsymbol{E}_n(\tau)\}^2$.
2. Calculate $\boldsymbol{D}_n(\tau)=\big(\boldsymbol{S}_n^{-1}\{\boldsymbol{e}_{n,1}(\tau),\tau\}-\widehat{\boldsymbol{\beta}}(\tau),\ldots,\boldsymbol{S}_n^{-1}\{\boldsymbol{e}_{n,p+1}(\tau),\tau\}-\widehat{\boldsymbol{\beta}}(\tau)\big)$, where $\boldsymbol{S}_n^{-1}(\boldsymbol{e},\tau)$ is defined as the solution to $\boldsymbol{S}_n(\boldsymbol{b},\tau)-\boldsymbol{e}=0$.
3. Estimate the asymptotic variance matrix of $n^{1/2}\{\widehat{\boldsymbol{\beta}}(\tau)-\boldsymbol{\beta}_0(\tau)\}$ by $n\{\boldsymbol{D}_n(\tau)\}^{\otimes 2}$.

Under conditionally random censoring, the self-consistent estimators and the martingale-based estimator for the model in Equation 4 take much more complex forms than those developed under the stronger censoring mechanism with either known censoring time or unconditionally independent censoring. Estimating the asymptotic variances of these estimators requires much more sophisticated twists of Huang's (2002) technique to address the challenge associated with unknown densities. A sample-based variance estimation procedure for Peng & Huang's (2008) estimator is available through adapting Sun et al.'s (2016) sample-based inference procedure for recurrent events data to the setting with randomly censored data.

2.4.2. Second-stage inference. The globally linear quantile regression model in Equation 4 provides a platform to explore the varying pattern of covariate effects across different quantile levels. Second-stage inference can be performed to address such interests. For example, one may estimate a functional of $\boldsymbol{\beta}_0(\cdot)$, say $\boldsymbol{\Psi}(\boldsymbol{\beta}_0)$, to provide a meaningful summary of covariate effects over a range of τ. It is often of interest to determine whether some covariates have constant effects so that a simpler model may be considered. In this case, the problem can be formulated as testing the null hypothesis $H_{0,j}: \beta_0^{(j)}(\tau) = \rho_0, \tau \in [\tau_L, \tau_U]$, where the superscript $^{(j)}$ indicates the jth component of a vector, and ρ_0 is an unspecified constant, $j = 2, \ldots,$ or $p+1$. Of note, accepting $H_{0,j}$ for all $j \in \{2, \ldots, p+1\}$ may indicate the adequacy of an AFT model. Peng & Huang (2008) presented second-stage inference procedures for estimating $\boldsymbol{\Psi}(\boldsymbol{\beta}_0)$ and testing H_0 under the model in Equation 4, which can be readily adapted to many other quantile regression settings.

3. QUANTILE REGRESSION IN COMPLEX SURVIVAL SETTINGS

In practice, survival data often involve complications beyond random censoring, such as truncation, competing risks, or semicompeting risks. Various methods have developed for quantile regression in more complex survival scenarios. In this section, we present a set of quantile regression methods developed for analyzing for doubly censored data with left truncation, competing risks data, and semicompeting risks data.

3.1. Quantile Regression with Doubly Censored Data with Left Truncation

Ji et al. (2012) proposed an extension of Peng & Huang's (2008) method to handle doubly censored data subject to left truncation. Such survival scenarios often arise in observational studies, where the event of interest can occur before study entry. Let T denote the event time of interest and C denote time to random right censoring. In addition, let L denote left censoring time, always observed, and A denote left truncation time. Define $X = L \vee (T \wedge C)$ and Δ as the censoring indicator, which equals 1 if $L < T \leq C$, 2 if $T \leq L$, and 3 if $T > C$, where $\vee$ is the maximum operator. When X is subject to left truncation by A, the observed data include n i.i.d. replicates of $(X', L', A', \delta', \boldsymbol{Z})$, denoted by $\{(X_i', L_i', A_i', \delta_i', \boldsymbol{Z}_i)\}_{i=1}^n$, where $\{X', L', A', \delta', \boldsymbol{Z}'\}$ follows the conditional distribution of $\{X, L, A, \delta, \boldsymbol{Z}\}$ given $X \geq A$. It is assumed that (L, C, A) is independent of T given $\boldsymbol{Z}$. We refer to such data as doubly censored data with left truncation. With $L = 0$, the data reduce to the usual randomly left truncated right censored data.

To estimate the model in Equation 4 with doubly censored data subject to left truncation, an estimating equation can be constructed based on the martingale structure underlying the observed survival data, namely, $M'(t) = N'(t) - \int_0^t R'(s)\mathrm{d}\Lambda_Y(s|\boldsymbol{Z})$, where $N'(t) = I(\log(X') \leq t, \delta' = 1)$, $R'(t) = I\{\log(L' \vee A') < t \leq \log(X')\}$ denoting an at-risk process, and $\Lambda_Y(\cdot|\boldsymbol{Z})$ denotes the cumulative hazard function of $Y \doteq \log(T)$ given $\boldsymbol{Z}$. It can be shown that $M'(t)$ is a martingale process. This fact suggests an estimating equation for $\boldsymbol{\beta}_0(\cdot)$,

$$n^{1/2}\boldsymbol{S}_n'(\boldsymbol{\beta}, \tau) \doteq n^{-1/2}\sum_{i=1}^n \boldsymbol{Z}_i\left(N_i'\{\boldsymbol{Z}_i^{\mathsf{T}}\boldsymbol{\beta}(\tau)\} - \int_0^\tau R'\{\boldsymbol{Z}_i^{\mathsf{T}}\boldsymbol{\beta}(u)\}\mathrm{d}H(u)\right) = 0. \qquad 12.$$

To obtain an estimator of $\boldsymbol{\beta}_0(\tau)$ based on Equation 12, denoted by $\widehat{\boldsymbol{\beta}}_{PH,*}(\tau)$, one may follow the algorithm for $\widehat{\boldsymbol{\beta}}_{\mathrm{PH}}(\tau)$ (presented in Section 2.3) with the objective function in Step 2 modified to

$$l_{k+1}^*(\boldsymbol{b}) = \sum_{i=1}^n \left|I(\Delta_i = 1)\log(X_i') - I(\Delta_i = 1)\boldsymbol{Z}_i^{\mathsf{T}}\boldsymbol{b}\right| + \left|Y^* - \sum_{l=1}^n(-I(\Delta_l = 1)\boldsymbol{Z}_l^{\mathsf{T}}\boldsymbol{b})\right|$$
$$+ \left|Y^* - \sum_{r=1}^n\left[(2\boldsymbol{Z}_r^{\mathsf{T}}\boldsymbol{b})\sum_{l=0}^k I\{\log(X_r') \geq \boldsymbol{Z}_r^{\mathsf{T}}\widehat{\boldsymbol{\beta}}_{PH,*}(\tau_l) \geq \log(L_r')\}\{H(\tau_{l+1}) - H(\tau_l)\}\right]\right|.$$

Theoretical properties, such as uniform consistency and weak convergence to a Gaussian process, can be established for $\widehat{\boldsymbol{\beta}}_{PH,*}(\tau)$ along similar lines to those established by Peng & Huang (2008).

3.2. Quantile Regression with Competing Risks Data

Competing risks data arise in scientific studies involving multiple types of failures that are mutually exclusive. For example, a cancer patient may die from tumor recurrence or nonrecurrence-related reasons. This gives rise to a competing risks scenario, where death from tumor recurrence and death from nonrecurrence-related reasons are two competing failure types.

We adopt a standard formulation of competing risks data. Let T_k denote the latent time to failure of type k ($k = 1, \ldots, K$). Define $T = \min(T_1, \ldots, T_K)$. Let ϵ denote the failure type corresponding to T (i.e., $T = T_\epsilon$), C denote independent censoring to T, and $\tilde{Z}$ denote a $p \times 1$ vector of covariates. Define $X = T \wedge C$, $\delta = I(T \leq C)\epsilon$, and $\boldsymbol{Z} = (1, \tilde{\boldsymbol{Z}}^\top)^\top$. Here $\wedge$ is the minimum operator and $I(\cdot)$ is the indicator function. The observed competing risks data consist of n i.i.d. replicates of $(X, \delta, \boldsymbol{Z})$, denoted by $\{(X_i, \delta_i, \boldsymbol{Z}_i),\ i = 1, \ldots, n\}$.

Analysis of competing risks data generally follows two different perspectives. One perspective focuses on crude quantities, such as the cumulative incidence function or cause-specific hazard function. Studying crude quantities for a failure type naturally accounts for the presence of competing risks from the other types of failure. The other perspective concerns net quantities defined upon latent failure times T_k. Inference on the latent failure time for a failure type, however, implicitly hypothesizes a setting where the other types of failure do not exist. Such a setting may be controversial but can be meaningful in some situations. For example, patient dropouts can be a competing risk for time to death but may be avoided by diligent follow-up efforts. When the elimination of other types of failures is not possible, competing risks analysis oriented to crude quantities would be more appropriate. In the following, we discuss quantile regression methods for competing risks data developed under these two different perspectives.

3.2.1. Competing risks quantile regression based on cumulative incidence functions.

Peng & Fine (2009) proposed to formulate competing risks quantile regression using cumulative incidence function, which is the cause-specific analog of the usual survival function for an event time. Specifically, the type-k cumulative incidence conditional quantile function is defined as $Q_k(\tau|\boldsymbol{Z}) \doteq \inf\{t :\ F_k(t|\boldsymbol{Z}) \geq \tau\}$, where $F_k(t|\boldsymbol{Z}) \doteq \Pr(T \leq t,\ \epsilon = k|\boldsymbol{Z})$ denotes the type-k cumulative incidence function ($k = 1, \ldots, K$). This quantity can be interpreted as the first time given covariate $\boldsymbol{Z}$ at which the probability of type-k failure having occurred exceeds τ, in the presence of other types of failures.

A competing risks quantile regression model based on type-k cumulative incidence function takes the form

$$Q_k(\tau|\boldsymbol{Z}) = \exp\{\boldsymbol{Z}^T\boldsymbol{\beta}_0(\tau)\},\quad \tau \in [\tau_L, \tau_U], \tag{13.}$$

where $\boldsymbol{\beta}_0(\tau)$ is a $(p+1) \times 1$ vector of unknown regression coefficients, and $0 \leq \tau_L \leq \tau_U < 1$. Under the model in Equation 13, the nonintercept coefficients in $\boldsymbol{\beta}_0(\tau)$ represent covariate effects on the τth cumulative incidence quantile, $Q_k(\tau|\boldsymbol{Z})$, which may change with τ. The $\exp(\cdot)$ function in Equation 13 can be replaced by any other monotone link function.

To estimate $\boldsymbol{\beta}_0(\tau)$ in the model in Equation 13, Peng & Fine (2009) proposed the following estimating equation:

$$n^{-1/2}\sum_{i=1}^{n}\boldsymbol{Z}_i\left(\frac{I\{X_i \leq \exp(\boldsymbol{Z}_i^T\boldsymbol{b})\}I(\delta_i = 1)}{\widehat{G}(X_i|\boldsymbol{Z}_i)} - \tau\right) = 0, \tag{14.}$$

where $\widehat{G}(\cdot|\boldsymbol{Z})$ is a reasonable estimate for $G(x|\boldsymbol{Z}) \doteq \Pr(C \geq x|\boldsymbol{Z})$, which can be obtained by following the discussions about $\hat{G}_U(\cdot|\boldsymbol{Z})$ in Section 2.3.4.

Solving Equation 14 can be reformulated as locating the minimizer of the convex L_1-type function,

$$\sum_{i=1}^{n} I(\delta_i = 1)\left|\frac{\log(X_i)}{\widehat{G}(X_i|\boldsymbol{Z}_i)} - \boldsymbol{b}^T\frac{\boldsymbol{Z}_i}{\widehat{G}(X_i|\boldsymbol{Z}_i)}\right| + \left|M^* - \boldsymbol{b}^T\sum_{l=1}^{n}\frac{-\boldsymbol{Z}_l I(\delta_l = 1)}{\widehat{G}(X_l|\boldsymbol{Z}_l)}\right| + \left|M^* - \boldsymbol{b}^T\sum_{k=1}^{n}(2\boldsymbol{Z}_k\tau)\right|,$$

where M^* is an extremely large positive number.

Peng & Fine (2009) showed that the resulting estimator is uniformly consistent in $\tau \in [\tau_L, \tau_U]$ and converges weakly to a tight mean-zero Gaussian process. They developed inference procedures about $\boldsymbol{\beta}_0(\tau)$ in the model in Equation 13, which follow similar lines to those presented in Section 2.4 for randomly censored data with known or unconditional independent censoring. Following the same framework, Sun et al. (2012) studied the model in Equation 13 for the competing risks setting with missing failure types, where the IPCW technique was used to deal with unobserved failure types under the missing at random assumption.

3.2.2. Quantile regression based on latent failure time distributions in the presence of competing risks. The analysis of competing risks data based on net quantities, such as the marginal distributions of T_ks ($k = 1, \ldots, K$), is complicated by their nonparametric nonidentifiability (Tsiatis 1975). Without loss of generality, we consider the situation with $K = 2$. This special case coincides with the typical dependent censoring scenario, where the dependent censoring event and the event of interest can be viewed as a pair of competing risks.

Concerning the latent failure times T_1 and T_2, one may consider the following quantile regression models:

$$Q_{T_k}(\tau|\boldsymbol{Z}) = \exp\{\boldsymbol{Z}^{\mathsf{T}}\boldsymbol{\beta}_{0,k}(\tau)\}, \quad \tau \in (0,1), \quad k = 1,2, \qquad 15.$$

where $\boldsymbol{\beta}_{0,k}(\tau)$ is an vector of unknown coefficients, representing covariate effects on $Q_{T_k}(\tau|\boldsymbol{Z})$. Here, $\exp(\cdot)$ can be replaced by another monotone link function, which may take different forms in the models for $Q_{T_1}(\tau|\boldsymbol{Z})$ and $Q_{T_2}(\tau|\boldsymbol{Z})$.

Ji et al. (2014) studied the estimation of the marginal quantile regression models in Equation 15 with competing risks data. To mitigate the identifiability issue, additional modeling is imposed for the dependence structure between T_1 and T_2. Specifically, it is assumed that

$$\Pr(T > t_1, D > t_2|\boldsymbol{Z}) = H\{\Pr(T > t_1|\boldsymbol{Z}), \Pr(D > t_2|\boldsymbol{Z})\}, \qquad 16.$$

where $H(\cdot, \cdot)$ is a known copula function, for example, the Clayton copula (Clayton 1978), i.e., $H(u,v) = \{u^{-r} + v^{-r} - 1\}^{-\frac{1}{r}}$, $r > 0$, and the Frank copula (Genest 1987), i.e., $H(u,v) = \log_r\{1 + \frac{(r^u-1)(r^v-1)}{r-1}\}$, $r > 0$ and $r \neq 1$. Here, r is a known copula parameter, which may be specified based on prior knowledge on the strength of the association between T_1 and T_2. In practice, one may perform a sensitivity analysis to obtain bounds for $Q_T(\tau|\boldsymbol{Z})$ by varying r in a plausible range.

To estimate $\boldsymbol{\beta}_{0,k}(\tau)$ in Equation 15, Ji et al. (2014) utilized the martingales associated with cause-specific hazard functions. Let $N_k(t) \doteq I(X \leq t, \epsilon = k)$ denote the counting process for T_k and define $M_k(t) = N_k(t) - \int_0^t I(X \geq u)\lambda_k^*(u|\boldsymbol{Z})\,\mathrm{d}u$, where $\lambda_k^*(t|\boldsymbol{Z}) = \lim_{h\to 0}\Pr(t \leq T_k < t + h, \epsilon = k|T_1 \geq t, T_2 \geq t; \boldsymbol{Z})/h$, which is the cause-specific hazard function for type-k failure. As shown by Kalbfleisch & Prentice (2002), $M_k(t)$ is a martingale with respect to the filtration, $\mathcal{F}_{t,k} = \{N_k(t), Y(t+), \boldsymbol{Z}\}$. This implies $E\{N_k(t) - \int_0^t I(X \geq s)\lambda_k^*(s|\boldsymbol{Z})\,\mathrm{d}s\} = 0$ for all $t \geq 0$. Under the models in Equations 15 and 16, it can be shown with stochastic integral

manipulations that

$$\int_0^t I(X \geq s)\lambda_k^*(s|\boldsymbol{Z})\,\mathrm{d}s$$
$$= \int_0^{F_{T_k}(t|\boldsymbol{Z})} I\{X \geq Q_{T_k}(u|\boldsymbol{Z})\}\phi_k\left(1-u,\ 1-\int_0^1 I[\exp\{\boldsymbol{Z}^T\boldsymbol{\beta}_{0,3-k}(v)\} \leq Q_{T_k}(u|\boldsymbol{Z})]\mathrm{d}v\right)\mathrm{d}u,$$

where $F_{T_k}(t|\boldsymbol{Z}) = \Pr(T_k \leq t|\boldsymbol{Z})$, $\phi_k(v_1, v_2) = \partial\log\{H(v_1, v_2)\}/\partial v_k$, and $k = 1, 2$. These facts motivate the estimating equations

$$n^{\frac{1}{2}}\boldsymbol{S}_n^{(k)}(\boldsymbol{\beta}_1, \boldsymbol{\beta}_2, \tau) = 0, \quad k = 1, 2, \tag{17.}$$

where $\boldsymbol{S}_n^{(k)}(\boldsymbol{\beta}_1, \boldsymbol{\beta}_2, \tau) = n^{-1}\sum_{i=1}^n \boldsymbol{Z}_i\{N_{ki}[\exp\{\boldsymbol{Z}_i^\mathsf{T}\boldsymbol{\beta}_k(\tau)\}] - \int_0^\tau I(X_i \geq \exp\{\boldsymbol{Z}_i^\mathsf{T}\boldsymbol{\beta}_{3-k}(u)\}) \times \phi_k(1-u, 1-\int_0^1 I\{\boldsymbol{Z}_i^T\boldsymbol{\beta}_{3-k}(v) \leq \boldsymbol{Z}_i^\mathsf{T}\boldsymbol{\beta}_k(u)\}\,\mathrm{d}v)\,\mathrm{d}u\}$.

Note that $\boldsymbol{\beta}_{0,k}(\tau)$ may not be identifiable for all $\tau \in (0, 1)$ due to censoring to T_k ($k = 1, 2$). Truncating the time scale by an upper bound, $\min(\exp\{\boldsymbol{Z}^\mathsf{T}\boldsymbol{\beta}_{0,1}(\tau_{U,1})\},\ \exp\{\boldsymbol{Z}^\mathsf{T}\boldsymbol{\beta}_{0,2}(\tau_{U,2})\})$, leads to a modified estimating equation,

$$n^{\frac{1}{2}}\boldsymbol{S}_n^{*(k)}(\boldsymbol{\beta}_1, \boldsymbol{\beta}_2, \tau) = 0, \quad k = 1, 2, \tag{18.}$$

where $\boldsymbol{S}_n^{*(k)}(\boldsymbol{\beta}_1, \boldsymbol{\beta}_2, \tau) = n^{-1}\sum_{i=1}^n \boldsymbol{Z}_i\{N_{ki}[\exp\{\boldsymbol{Z}_i^\mathsf{T}\boldsymbol{\beta}_k(\tau)\}]I\{\log(X_i) \leq \boldsymbol{Z}_i^\mathsf{T}\boldsymbol{\beta}_{3-k}(\tau_{U,3-k})\} - \int_0^\tau I(X_i \geq \exp\{\boldsymbol{Z}_i^\mathsf{T}\boldsymbol{\beta}_k(u)\})I\{\boldsymbol{Z}_i^\mathsf{T}\boldsymbol{\beta}_k(u) \leq \boldsymbol{Z}_i^\mathsf{T}\boldsymbol{\beta}_{3-k}(\tau_{U,3-k})\} \times \phi_k(1-u, 1-\int_0^{\tau_{U,3-k}} I\{\boldsymbol{Z}_i^\mathsf{T}\boldsymbol{\beta}_{3-k}(v) \leq \boldsymbol{Z}_i^\mathsf{T}\boldsymbol{\beta}_k(u)\}\,\mathrm{d}v)\,\mathrm{d}u\}$.

Equation 18 may be solved via an iterative algorithm:

1. Set $m = 0$. Choose the initial value $\hat{\boldsymbol{\beta}}_2^{[m]}(\tau), \tau \in (0, \tau_{U,2}]$.
2. Solve $\boldsymbol{S}_n^{*(1)}(\boldsymbol{\beta}_1, \hat{\boldsymbol{\beta}}_2^{[m]}, \tau) = 0$ for $\hat{\boldsymbol{\beta}}_1^{[m+1]}(\tau), \tau \in (0, \tau_{U,1}^{[m+1]}]$. Update $\tau_{U,1}$ with $\tau_{U,1}^{[m+1]}$.
3. Solve $\boldsymbol{S}_n^{*(2)}(\hat{\boldsymbol{\beta}}_1^{[m+1]}, \boldsymbol{\beta}_2, \tau) = 0$ for $\hat{\boldsymbol{\beta}}_2^{[m+1]}(\tau), \tau \in (0, \tau_{U,2}^{[m+1]}]$. Update $\tau_{U,2}$ with $\tau_{U,2}^{[m+1]}$.
4. Let $m = m + 1$. Repeat steps 2 and 3 until convergence criteria are met.

Here, the initial value in step 1 can be set as Peng & Huang's (2008) estimator, which treats T_1 and T_2 as independent. The equations in steps 2–3 can be solved by L_1 minimization problems along similar lines to those presented by Peng & Huang (2008).

Asymptotic properties were established for the resulting estimators of $\boldsymbol{\beta}_{0,k}$ ($k = 1, 2$), including uniform consistency and weak convergence to a Gaussian process. Inference can be conducted through a standard bootstrapping procedure.

3.3. Quantile Regression with Semicompeting Risks Data

"Semicompeting risks" (Fine et al. 2001) refers to a situation in which time to a nonterminal event (e.g., a nonfatal disease landmark event) can be censored by time to a terminal event (e.g., death or dropout) but not vice versa. Let T_1, T_2, and C denote time to the nonterminal event, time to the terminal event, and time to random censoring, respectively. Let $\tilde{\boldsymbol{Z}}$ be a $p \times 1$ vector of covariates and $\boldsymbol{Z} = (1, \tilde{\boldsymbol{Z}}^\mathsf{T})^\mathsf{T}$. Define $X = T_1 \wedge T_2 \wedge C$, $Y = T_2 \wedge C$, $\delta = I(T_1 < Y)$, and $\eta = I(T_2 < C)$. The standard semicompeting risks data consist of n replicates of $(X, Y, \delta, \eta, \tilde{\boldsymbol{Z}})$, denoted by $\{(X_i, Y_i, \delta_i, \eta_i, \tilde{\boldsymbol{Z}}_i),\ \ i = 1, \ldots, n\}$. In a standard semicompeting risks setting, T_2 is only subject to random censoring by C; thus, quantile regression for T_2 can follow the approaches developed for randomly censored data (see Section 2).

Semicompeting risks methods are usually focused on the inference about T_1, which is complicated by the dependent censoring by T_2. Intuitively, one may first coerce semicompeting risks data

into classic competing risks data by ignoring the extra information on T_2 when $\delta = 1$, and then apply quantile regression approaches developed for competing risks data. For example, targeting crude quantities for the nonterminal event, one can directly perform competing risks cumulative incidence quantile regression presented in Section 3.2.1. Of note, this approach does not incur information loss from only using the competing risks portion of the data. This is because when $\delta = 1$, the cumulative incidence function for the nonterminal event, by definition, does not involve the extra information on the terminal event after the occurrence of the nonterminal event. An exception arises when left truncation is present. In that case, the semicompeting risks data are observable only when $Y > L$, where L is a known left truncation time. Coercing semicompeting risks data into competing risks data induces artificial left truncation defined as $X > L$, thereby leading to information loss.

Li & Peng (2011) developed an extension of Peng & Fine's (2009) method for competing risks cumulative incidence quantile regression tailored to semicompeting risks data subject to left truncation. In this case, the observed data include n i.i.d. replicates of $(X^*, Y^*, \delta^*, \eta^*, L^*, \boldsymbol{Z}^*)$, which follow the conditional distribution of $(X, Y, \delta, \eta, L, \boldsymbol{Z})$ given $L < Y$. Assume the cumulative incidence quantile regression model for T_1, which is the model in Equation 13 with $k = 1$. The basic estimation idea is to employ the IPCW technique with an inverse weight derived to properly account for both censoring by C and left truncation Y. Under the assumption that (L, C) is independent of $(T_1, T_2, \boldsymbol{Z})$, an estimating equation is given by

$$n^{-1/2} \sum_{i=1}^{n} \boldsymbol{Z}_i^* \left[\frac{I\{X_i^* \le \exp(\boldsymbol{Z}_i^{*T} \boldsymbol{b}), \delta_i^* = 1, \eta_i^* = 1\}}{\hat{W}(Y_i^*, \boldsymbol{Z}_i^*)} - \tau \right] = 0, \qquad 19.$$

where $\hat{W}(y, \boldsymbol{z}) = \hat{G}(y)/\hat{G}(\boldsymbol{z})$ with

$$\hat{\alpha}(\boldsymbol{z}) = \int_0^v \hat{S}_{T_2}(u|\boldsymbol{z}) \hat{F}_L(\mathrm{d}u), \quad \hat{G}(y) = \frac{1}{n} \sum_{i=1}^{n} \frac{I(L_i^* < y \le Y_i^*) \hat{\alpha}(\boldsymbol{Z}_i^*)}{\hat{S}_{T_2}(y - |\boldsymbol{Z}_i^*)}.$$

Here $\hat{F}_L(y)$ represents the Lynden-Bell estimator of $F_L(y) \doteq P(L \le y)$, and $\hat{S}_{T_2}(u|\boldsymbol{z})$ is an adequate estimator of $P(T_2 > u|\boldsymbol{z})$. In practice, given T_2 is only subject to random right censoring by C and random left truncation by L, $\hat{S}_{T_2|\boldsymbol{Z}=\boldsymbol{z}}(t)$ may be obtained by using any existing regression method for left truncated and right censored data, such as the Cox PH model. After obtaining $\hat{W}(Y_i^*, \boldsymbol{Z}_i^*)$, Equation 19 can be solved by an algorithm similar to that presented for Equation 14. Desirable theoretical properties, including uniform consistency and weak convergence to a Gaussian process, can also be established for the resulting estimator.

When interest lies in net quantities related to the latent time to nonterminal event T_1, utilizing the extra information in semicompeting risks data (beyond its competing risks portion) generally leads to better identifiability as well as improved statistical efficiency. Along these lines, Li & Peng (2015) developed a quantile regression method tailored to study the conditional quantile of T_1 in the semicompeting risks setting. Specifically, Li & Peng (2015) assumed the following models:

$$\Pr(T_1 > s, T_2 > t \mid \boldsymbol{Z}) = C\{1 - F_{T_1}(s|\boldsymbol{Z}), 1 - F_{T_2}(t|\boldsymbol{Z}); g(\bar{\boldsymbol{Z}}^T \boldsymbol{r}_0)\}, \qquad 20.$$

$$Q_{T_1}(\tau|\boldsymbol{Z}) = \exp\{\boldsymbol{Z}^T \boldsymbol{\beta}_0(\tau)\}, \quad Q_{T_2}(\tau \mid \boldsymbol{Z}) = \exp\{\boldsymbol{Z}^T \boldsymbol{\alpha}_0(\tau)\}, \quad 0 < \tau < 1, \qquad 21.$$

where $\bar{\boldsymbol{Z}}$ is a subvector of $\boldsymbol{Z}$ or $\boldsymbol{Z}$ itself, $C(\cdot, \cdot; \alpha)$ is a known copula function with a given copula parameter α, and $g(\cdot)$ is a known function. In the copula model in Equation 20, the unknown parameter $\boldsymbol{r}_0$ depicts how covariates may influence the copula parameter, which is often closely linked to the association between T_1 and T_2. In Equation 21, the nonintercept coefficients in $\boldsymbol{\beta}_0(\tau)$

and $\boldsymbol{\alpha}_0(\tau)$ represent covariate effects on the τth quantile of T_1 and T_2, respectively, which are permitted to change with τ. When these coefficients are constant over τ, the models in Equation 21 reduce to AFT models for T_1 and T_2.

To estimate the models in Equation 20 and Equation 21, a useful fact is that Equation 20 implies

$$\Pr(X > t \mid Y > t, \boldsymbol{Z}) = K_A\{\Pr(T_1 > s|\boldsymbol{Z}), \Pr(T_2 > t|\boldsymbol{Z}), g(\tilde{\boldsymbol{Z}}^{\mathsf{T}}\boldsymbol{r}_0)\}, \quad t > 0, \tag{22.}$$

$$\Pr(X \le s \mid Y > t, \boldsymbol{Z}) = K_B\{\Pr(T_1 > s|\boldsymbol{Z}), \Pr(T_2 > t|\boldsymbol{Z}), g(\tilde{\boldsymbol{Z}}^{\mathsf{T}}\boldsymbol{r}_0)\}, \quad s \le t, \tag{23.}$$

where $K_A(u, v, \theta) = C(u, v; \alpha)/v$ and $K_B(u, v, \alpha) = \{v - C(u, v; \alpha)\}/v$. In addition, the model assumptions in Equation 21 imply $\Pr(T_1 \le \exp\{\boldsymbol{Z}^T\boldsymbol{\beta}_0(\tau)\} \mid \boldsymbol{Z}) = \tau$ and $\Pr(T_2 \le t \mid \boldsymbol{Z})) = \int_0^1 I\big[t \ge \exp\{\boldsymbol{Z}^T\boldsymbol{\alpha}_0(u)\}\big]\mathrm{d}u$. Li & Peng (2015) utilized these results to construct the following estimating equations:

$$n^{-1/2}\sum_{i=1}^{n}\tilde{\boldsymbol{Z}}_i I\{\tilde{\boldsymbol{Z}}_i^T\boldsymbol{\beta}(\tau) \le \tilde{\boldsymbol{Z}}_i^T\hat{\boldsymbol{\alpha}}(\tau_{U,2})\}P_i(\boldsymbol{\beta}, \hat{\boldsymbol{\alpha}}, \boldsymbol{r}, \tau) = 0, \quad n^{-1/2}\sum_{i=1}^{n}\int_{\tau_a}^{\tau_b}\tilde{\tilde{\boldsymbol{Z}}}_i Q_i(\boldsymbol{\beta}, \hat{\boldsymbol{\alpha}}, \boldsymbol{r}, \tau) = 0,$$

where $\hat{\boldsymbol{\alpha}}(\cdot)$ is Peng & Huang's (2008) estimator of $\boldsymbol{\alpha}_0(\cdot)$ given that T_2 is only subject to random censoring by C, $\tau_{U,2}$ is an upper bound of a τ-range where $\alpha_0(\tau)$ is identifiable, and

$$\begin{aligned}
P_i(\boldsymbol{\beta}, \boldsymbol{\alpha}, \boldsymbol{r}, \tau) &= I\{\log X_i > \tilde{\boldsymbol{Z}}_i^T\boldsymbol{\beta}(\tau)\} - I\{\log Y_i > \tilde{\boldsymbol{Z}}_i^T\boldsymbol{\beta}(\tau)\} \\
&\quad \times K_A\left\{\tau, \int_0^{\tau_{U,2}} I\{\tilde{\boldsymbol{Z}}_i^T\boldsymbol{\beta}(\tau) \ge \tilde{\boldsymbol{Z}}_i^T\boldsymbol{\alpha}(u)\}\mathrm{d}u, g(\tilde{\tilde{\boldsymbol{Z}}}_i^T\boldsymbol{r})\right\}, \\
Q_i(\boldsymbol{\beta}, \boldsymbol{\alpha}, \boldsymbol{r}, \tau) &= \int_{t\in(0,\infty)} I\big\{\tilde{\boldsymbol{Z}}_i^T\boldsymbol{\beta}(\tau) \le \log t \le \tilde{\boldsymbol{Z}}_i{}^T\boldsymbol{\alpha}(\tau_{U2}) \wedge \log Y_i\big\} \\
&\quad \times \left(I\big\{\log X_i \le \tilde{\boldsymbol{Z}}_i^T\boldsymbol{\beta}(\tau)\big\} - K_B\left[\tau, \int_0^{\tau_{U,2}} I\big\{\log t \ge \tilde{\boldsymbol{Z}}_i^T\boldsymbol{\alpha}(u)\big\}\mathrm{d}u, g(\tilde{\tilde{\boldsymbol{Z}}}_i^T\boldsymbol{r})\right]\right)\mathrm{d}t.
\end{aligned}$$

To compute $Q_i(\boldsymbol{\beta}, \hat{\boldsymbol{\alpha}}, \boldsymbol{r}, \tau)$, one only needs to evaluate the integration over $t \in (0, \max_{i=1}^n Y_i \wedge \exp\{\boldsymbol{Z}_i^{\mathsf{T}}\hat{\boldsymbol{\alpha}}(\tau_{U,2})\}$. Confining $\boldsymbol{\beta}(\cdot)$ to be a cadlag step function, the integrand in $Q_i(\boldsymbol{\beta}, \hat{\boldsymbol{\alpha}}, \boldsymbol{r}, \tau)$ is a piecewise constant function of τ, and hence $Q_i(\boldsymbol{\beta}, \hat{\boldsymbol{\alpha}}, \boldsymbol{r}, \tau)$ can be calculated as a finite sum. Li & Peng (2015) presented an iterative algorithm to solve these estimating equations, and they showed that the resulting estimator of $\boldsymbol{r}_0$ is consistent and asymptotic normal. Desirable theoretical properties, including uniform consistency and weak convergence to a Gaussian process, were established for the resulting estimator of $\boldsymbol{\beta}_0(\tau)$ for $\tau \in [\nu_1, \tau_{U,1}]$, where $0 < \nu_1 < \tau_{U,1} < 1$.

4. QUANTILE REGRESSION AND ITS ADAPTATIONS FOR RECURRENT EVENTS DATA

Recurrent events data are frequently encountered in clinical or epidemiological studies when the event of interest, such as infection and hospitalization, can occur repeatedly over time. Consider a general recurrent events data setting, where the observation of recurrent events is subject to an observation window specified as a time interval $(L, R]$ (Nelson 2003). The counting process for the observed recurrent events is given by $N^{\mathrm{re}}(t) = \sum_{j=1}^{\infty} I(L \le T_j^{(i)} \le t \wedge R)$, where $T^{(j)}$ denotes time to the jth recurrent event ($j = 1, 2, \ldots$), and the at-risk process is given by $Y^{\mathrm{re}}(t) = I(L < t \le R)$. Let $\tilde{\boldsymbol{Z}}$ be a $p \times 1$ vector of covariates and $\boldsymbol{Z} = (1, \tilde{\boldsymbol{Z}}^{\mathsf{T}})^{\mathsf{T}}$. The observed recurrent events data include n i.i.d. replicates of $N^{\mathrm{re}}(\cdot)$, $\boldsymbol{Z}$, L, and R, denoted by $\{N_i^{\mathrm{re}}(\cdot), \boldsymbol{Z}_i, L_i, R_i\}_{i=1}^n$. In this section, we introduce three different ways to apply or adapt quantile regression to recurrent events data.

4.1. Quantile Regression of Recurrent Event Gap Time

Luo et al. (2013) proposed to model the gap time between recurrent events, namely, $G_{i,j} \doteq T_i^{(j)} - T_i^{(j-1)}$. In this approach, it is assumed that conditioning on $\boldsymbol{Z}_i$ and a nonnegative subject-specific frailty variable γ_i, $N_i^{\mathrm{re}}(\cdot)$ is a renewal process, and furthermore,

$$Q_{G_{i,j}}(\tau|\boldsymbol{Z}_i) = \exp\{\boldsymbol{Z}_i^{\mathsf{T}}\boldsymbol{\beta}_0(\tau)\}, \quad \tau \in (0, \tau_U]. \tag{24.}$$

Consider the case where $L_i = 0$ and R_i is independent of γ_i and $\{T_i^{(j)}\}_{j=1}^{\infty}$ given $\boldsymbol{Z}_i$. Let $m_i = N_i^{\mathrm{re}}(R_i)$, $m_i^* = \max(m_i - 1, 1)$ and $\Delta_i = I(m_i > 1)$. Define $X_{i,j} = G_{i,j}$ if $j < m_i$ and $X_{i,j} = R_i - T_i^{(m_i-1)}$ if $j = m_i$. Define $N_{i,j}(t) = I(G_{i,j} \le t, \Delta_i = 1)$, $R_{i,j}(t) = I(G_{i,j} \ge t)$, $H(x) = -\log(1 - x)$. Note that uncensored gap times, $\{X_{i,j}, j = 1, \ldots, m_i - 1\}$, combined with the censored first gap time, $X_{i,1}$ with $\Delta_i = 0$, can be viewed as clustered event times subject to random censoring. Under this view and by adapting the estimation framework of Peng & Huang (2008), Luo et al. (2013) proposed the following estimating equation for the model in Equation 24:

$$n^{-1/2}\sum_{i=1}^{n}\boldsymbol{Z}_i\left[N_i^*(\exp\{\boldsymbol{Z}_i^{\mathsf{T}}\boldsymbol{\beta}(\tau)\}) - \int_0^{\tau} R_i^*(\exp\{\boldsymbol{Z}_i^{\mathsf{T}}\boldsymbol{\beta}(u)\})\mathrm{d}H(u)\right] = 0, \tag{25.}$$

where $N_i^*(t) = (m_i^*)^{-1}\sum_{j=1}^{m_i^*} N_{i,j}(t)$ and $R_i^*(t) = (m_i^*)^{-1}\sum_{j=1}^{m_i^*} R_{i,j}(t)$. An efficient algorithm to solve Equation 25 can be developed along the lines of Peng & Huang (2008).

4.2. Generalized Accelerated Recurrence Time Model

Huang & Peng (2009) and Sun et al. (2016) adopted a different strategy to adapt quantile regression modeling to recurrence events data. The main idea is to utilize the concept of time to expected frequency, which is a generalized version of conditional quantile that fits the recurrent events setting. Specifically, time to expected frequency is defined as $\tau_{\boldsymbol{Z}}(u) \doteq \inf\{t \ge 0 : \mu_{\boldsymbol{Z}}(t) \ge u\}$ for $u > 0$, where $\tilde{N}(t) = \sum_{j=1}^{\infty} I(T^{(j)} \le t)$ and $\mu_{\boldsymbol{Z}}(t) = E\{\tilde{N}(t)|\boldsymbol{Z}\}$. It is easy to see that when the event of interest is not recurrent (i.e., $T^{(j)} = \infty$ for $j \ge 2$), $\tau_{\boldsymbol{Z}}(u)$ becomes the conditional quantile $Q_{T^{(1)}}(\tau|\boldsymbol{Z})$. With recurrent events data, an adaptation of quantile regression modeling is to formulate covariate effects on $\tau_{\boldsymbol{Z}}(u)$. This leads to the generalized accelerated recurrence time model, which is given by

$$\tau_{\boldsymbol{Z}}(G(u)) = \exp\{\boldsymbol{Z}^{\mathsf{T}}\boldsymbol{\beta}_0(u)\}, \quad u \in (0, U], \tag{26.}$$

where $G(\cdot)$ is a known positive increasing function, the nonintercept coefficients in $\boldsymbol{\beta}_0(u)$ represent covariate effects on time to expected frequency $G(u)$, and $U > 0$ is a prespecified constant.

The estimation of the model in Equation 26 is facilitated by the counting process representation of Equation 26 justified in Sun et al. (2016). That is, the model in Equation 26 is equivalent to

$$E\{N^{\mathrm{re}}(\exp\{\boldsymbol{Z}^{\mathsf{T}}\boldsymbol{\beta}_0(u)\})|\boldsymbol{Z}\} = E\left\{\int_0^u Y^{\mathrm{re}}(\exp\{\boldsymbol{Z}^{\mathsf{T}}\boldsymbol{\beta}_0(s)\})g(s)\mathrm{d}s|\boldsymbol{Z}\right\}, \quad u \in (0, U], \tag{27.}$$

where $g(u) = \mathrm{d}G(u)/\mathrm{d}u$. This motivates a stochastic integral equation taking the form:

$$n^{-1/2}\sum_{i=1}^{n}\boldsymbol{X}_i\left\{N_i^{\mathrm{re}}(\exp\{\boldsymbol{X}_i^{\mathsf{T}}\boldsymbol{\beta}(u)\}) - \int_0^u Y_i^{\mathrm{re}}(\exp\{\boldsymbol{X}_i^{\mathsf{T}}\boldsymbol{\beta}(s)\})g(s)ds\right\} = 0, \quad u \in (0, U]. \tag{28.}$$

As commented on by Sun et al. (2016), the theoretical and computational framework of Peng & Huang (2008) can be readily extended to study the recurrent events model in Equation 26. The algorithm to solve Equation 28 is very similar to that for the martingale-based estimator of

Peng & Huang (2008) (see Section 2). The key modifications include adopting a grid on the frequency scale (instead of the τ scale), $\{0 = u_0 < u_1 < \cdots < u_{L(n)} = U\}$, and replacing the objective function in Step 2 by

$$l_k(\boldsymbol{b}) = \sum_{i=1}^{n}\sum_{j=1}^{\infty} I(L_i \le T_i^{(j)} \le R_i)\left|\log T_i^{(j)} - \boldsymbol{X}_i^{\top}\boldsymbol{b}\right| + \left|R^* - \left\{\sum_{i=1}^{n}\sum_{j=1}^{\infty} I(L_i \le T_i^{(j)} \le R_i)(-\boldsymbol{X}_i)^{\top}\boldsymbol{b}\right\}\right|$$
$$+ \left|R^* - \left\{\sum_{i=1}^{n} 2\boldsymbol{X}_i^{\top}\boldsymbol{b}\sum_{m=0}^{k-1} Y_i(\exp\{\boldsymbol{X}_i^{\top}\hat{\boldsymbol{\beta}}(u_m)\})\int_{u_m}^{u_{m+1}} g(s)\mathrm{d}s,\right\}\right|,$$

where R^* is an extremely large number. Theoretical arguments for Peng & Huang's (2008) estimator can also be generalized to establish the asymptotic properties of the estimator derived based on Equation 28, including the uniform consistency for $u \in [v, U]$, where $0 < v < U$, and weak convergence to a Gaussian process at the root n rate.

4.3. Quantile Regression of Individual Recurrent Risk Measure

More recently, Ma et al. (2020) proposed quantile regression of a sensible individual risk measure formulated upon the intensity process of recurrent events. Let $\tilde{N}(t) \doteq \sum_{j=1}^{\infty} I(T^{(j)} \le t)$ denote the underlying recurrent event process. Ma et al. (2020) assumed that given a nonnegative random variable γ_i, $\tilde{N}_i(t)$ is a nonstationary Poisson process with the intensity function

$$\lambda(t|\gamma_i) = \gamma_i \cdot \lambda_0(t). \tag{29.}$$

Here $\lambda_0(t)$ stands for an unknown baseline intensity function, which is nonnegative and continuous, and is subject to the constraint, $\int_0^{v^*} \lambda_0(t)\mathrm{d}t = 1$, with a predetermined constant v^*. This constraint is necessary for the purpose of model identifiability.

Under the model in Equation 29, γ_i captures the scale shift of subject i's intensity process from the unknown baseline intensity $\lambda_0(t)$. A special case of the model in Equation 29 is the semiparametric multiplicative intensity model of Wang et al. (2001), where $\gamma_i = \xi_i \exp(\tilde{\boldsymbol{Z}}_i^{\top}\boldsymbol{b}_0)$, and ξ_i is an unobservable frailty. This connection suggests that γ_i can serve as a sensible measure of the latent subject-specific risk of recurrent events, which may naturally account for both observed covariates and unobservable frailty.

Ma et al. (2020) proposed to use quantile regression to explore the heterogeneity in γ_i which quantifies the subject-specific risk of recurrent events. Specifically, it is assumed that

$$Q_{\gamma_i}(\tau|\boldsymbol{Z}_i) = \exp\{\boldsymbol{Z}_i^{\top}\boldsymbol{\beta}_0(\tau)\}. \tag{30.}$$

The nonintercept coefficients in $\boldsymbol{\beta}_0(\tau)$ represent covariate effects on the τth quantiles of γ_i.

A main challenge to estimating the model in Equation 30 is that γ_is are not observed. Considering the setting with $L_i = 0$ and assuming R_i is independent of $\tilde{N}_i(\cdot)$ given γ_i, and R_i is independent of γ_i given $\boldsymbol{Z}_i$, Ma et al. (2020) employed the principle of conditional score (Stefanski & Carroll 1987) and proposed the estimating equation

$$n^{1/2}\boldsymbol{S}_n(\boldsymbol{\beta}, \hat{\mu}, \tau) = 0, \tag{31.}$$

where $\boldsymbol{S}_n(\boldsymbol{\beta}, \mu, \tau) \doteq n^{-1}\sum_{i=1}^{n}\int_r \boldsymbol{Z}_i \cdot \psi_\tau\{\log(r) - \boldsymbol{Z}_i^{\top}\boldsymbol{\beta}(\tau)\} f\{r|m_i, C_i, \boldsymbol{Z}_i; \boldsymbol{\beta}(\cdot), \mu(\cdot)\}\mathrm{d}r$ and $\hat{\mu}(t) = \exp\{\hat{H}(t)\}$ with

$$\hat{H}(t) = -\int_t^{v^*} \frac{\sum_{i=1}^{n}\mathrm{d}N_i^{\mathrm{re}}(s)}{\sum_{i=1}^{n} I(R_i \ge s)N_i^{\mathrm{re}}(s)}.$$

Here, $\psi_\tau(v) = \tau - I(v < 0)$, and

$$f\{\gamma|m, C, \boldsymbol{X}; \boldsymbol{\beta}(\cdot), \mu(\cdot)\} = \frac{\rho\{m|\gamma, C; \mu(\cdot)\}g\{\gamma|\boldsymbol{X}; \boldsymbol{\beta}(\cdot)\}}{\int_r \rho\{m|r, C; \mu(\cdot)\}g\{r|\boldsymbol{X}; \boldsymbol{\beta}(\cdot)\}\mathrm{d}r},$$

where

$$\rho\{m|\gamma, C; \mu(\cdot)\} = \frac{\{\gamma\mu(C)\}^m}{m!}\exp\{-\gamma\mu(C)\} \qquad 32.$$

and

$$g\{\gamma|\boldsymbol{X}; \boldsymbol{\beta}(\cdot)\} = \lim_{\delta\to 0}\frac{\delta}{\exp\{\boldsymbol{X}^\top\boldsymbol{\beta}(\tau_\gamma + \delta)\} - \exp\{\boldsymbol{X}^\top\boldsymbol{\beta}(\tau_\gamma)\}},$$

with

$$\tau_\gamma = \{\tau \in (0, 1) : \exp\{\boldsymbol{X}^\top\boldsymbol{\beta}(\tau)\} = \gamma\}.$$

It can be shown that $f\{\gamma|m, C, \boldsymbol{X}; \boldsymbol{\beta}_0(\cdot), \mu_0(\cdot)\}$ denotes the conditional density of γ given m, C and $\boldsymbol{X}$ under the assumed models, and hence $E[\boldsymbol{S}_n(\boldsymbol{\beta}_0, \mu_0, \tau)] = 0$.

To solve Equation 31, Ma et al. (2020) approximated $\boldsymbol{\beta}(\tau)$ by using splines with $K(n)$ knots and developed an iterative algorithm to find an estimate for the $\boldsymbol{\beta}_0(\tau)$ in the model in Equation 30 based on Equation 31. The details are omitted here. Under certain regularity conditions, the resulting estimator was shown to be uniformly consistent for $\tau \in [\zeta_1, \zeta_2]$, where $0 < \zeta_1 < \zeta_2 < 1$. Weak convergence to a Gaussian process was also established.

5. ILLUSTRATIONS OF QUANTILE REGRESSION FOR SURVIVAL DATA

5.1. An Example of Quantile Regression Analysis with Randomly Censored Data

We use a data set from a dialysis study that investigated predictors of mortality in a cohort of 191 incident dialysis patients with chronic renal failure, aged 20 years and older, who started on chronic hemodialysis or peritoneal dialysis therapy between July 1996 and August 1997, recruited from the metro Atlanta area (Kutner et al. 2002). Of particular interest is a risk factor on symptoms of RLS, which negatively affects quality of life and mortality risk as evidenced by prior studies. In this study, baseline measures were collected between 1996 and 1997 and vital status was monitored to December 2005. In this data set, the survival times T of 35% of dialysis patients were censored due to renal transplant or the end of the study.

Figure 1 plots the Kaplan–Meier curves for survival time stratified by the binary variable indicating moderate to severe RLS symptoms versus mild RLS symptoms (denoted by BLEGS). It is noted that the 25th percentiles of survival time for the severe RLS group and the mild RLS groups are 0.95 versus 2.45 years, which are statistically significantly different. The 75th survival time percentiles for these two groups are rather similar, both between 7 and 8 years. This observation suggests that BLEGS may have an inhomogeneous effect on the distribution or quantile function of T. We next consider BLEGS, along with other potential predictors including patient's age (AGE), the indicator of fish consumption over the first year of dialysis (FISHH), the indicator of baseline hemodialysis dialysis modality (BHDPD), the indicator of education equal or higher than college (HIEDU), and the indicator of being black (BLACK). We fit the data with the standard Cox PH model and AFT model. In **Table 1**, we present the estimation results including the estimated coefficients and the associated p-values. It is shown that both the Cox PH model

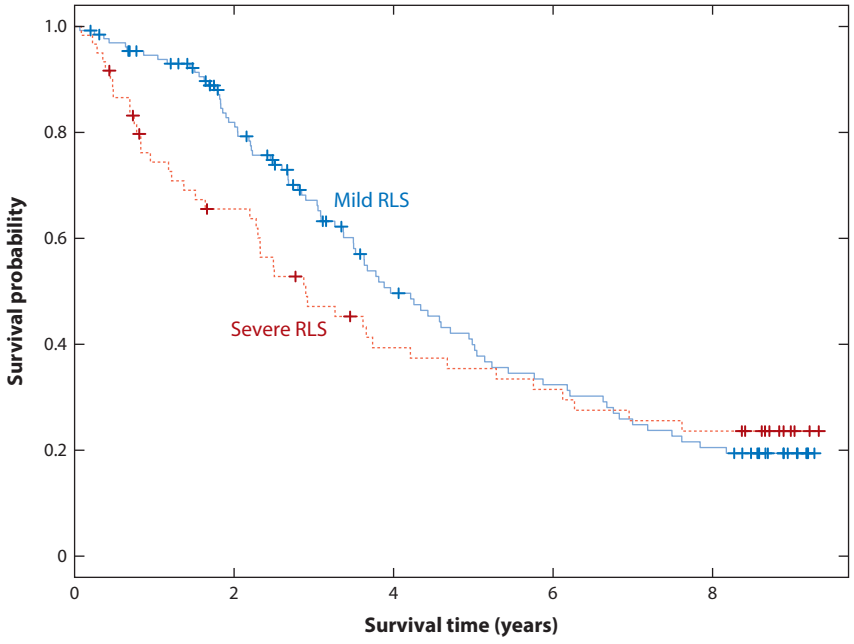

Figure 1

The dialysis example: Kaplan–Meier curves of survival time stratified by the status of RLS symptoms. Adapted with permission from Peng & Huang (2008), figure 1. Abbreviation: RLS, restless leg syndrome.

and the AFT model do not suggest a significant effect of BLEGS on dialysis survival, though **Figure 1** demonstrates its potential influence on the lower part of the survival distribution.

We next conduct quantile regression based on the model in Equation 4 using Peng & Huang's (2008) method for the same data set. **Figure 2** displays Peng & Huang's (2008) estimator of $\boldsymbol{\beta}_0(\tau)$ along with 95% pointwise confidence intervals. In **Figure 2**, we observe that the coefficient for BLEGS diminishes gradually with τ, whereas estimates for the other coefficients seem to be fairly constant. We apply the second-stage inference to formally investigate the constancy of each coefficient. The results confirm our observation from **Figure 1**, suggesting a varying effect of BLEGS and constant effects of the other covariates. This may lead to an interesting scientific

Table 1 Results from fitting the Cox PH model and AFT model to the dialysis data set

	Cox Model		AFT Model	
	Coefficient	***p*-Value**	**Coefficient**	***p*-Value**
AGE	0.059	<0.001	−0.035	<0.001
FISHH	−0.831	<0.001	0.485	<0.001
BHDPD	0.837	<0.001	−0.473	<0.001
BLEGS	0.264	0.197	−0.173	0.232
HIEDU	0.625	0.009	0.364	0.024
BLACK	−1.014	<0.001	0.591	<0.001

Abbreviations: AFT, accelerated failure time; AGE, patient age; BHDPD, indicator of baseline hemodialysis dialysis modality; BLACK, indicator of being black, BLEGS, binary variable indicating moderate to severe RLS symptoms versus mild RLS symptoms; FISHH, indicator of fish consumption over the first year of dialysis; HIEDU, indicator of education equal to or higher than college; PH, proportional hazards; RLS, restless leg syndrome.

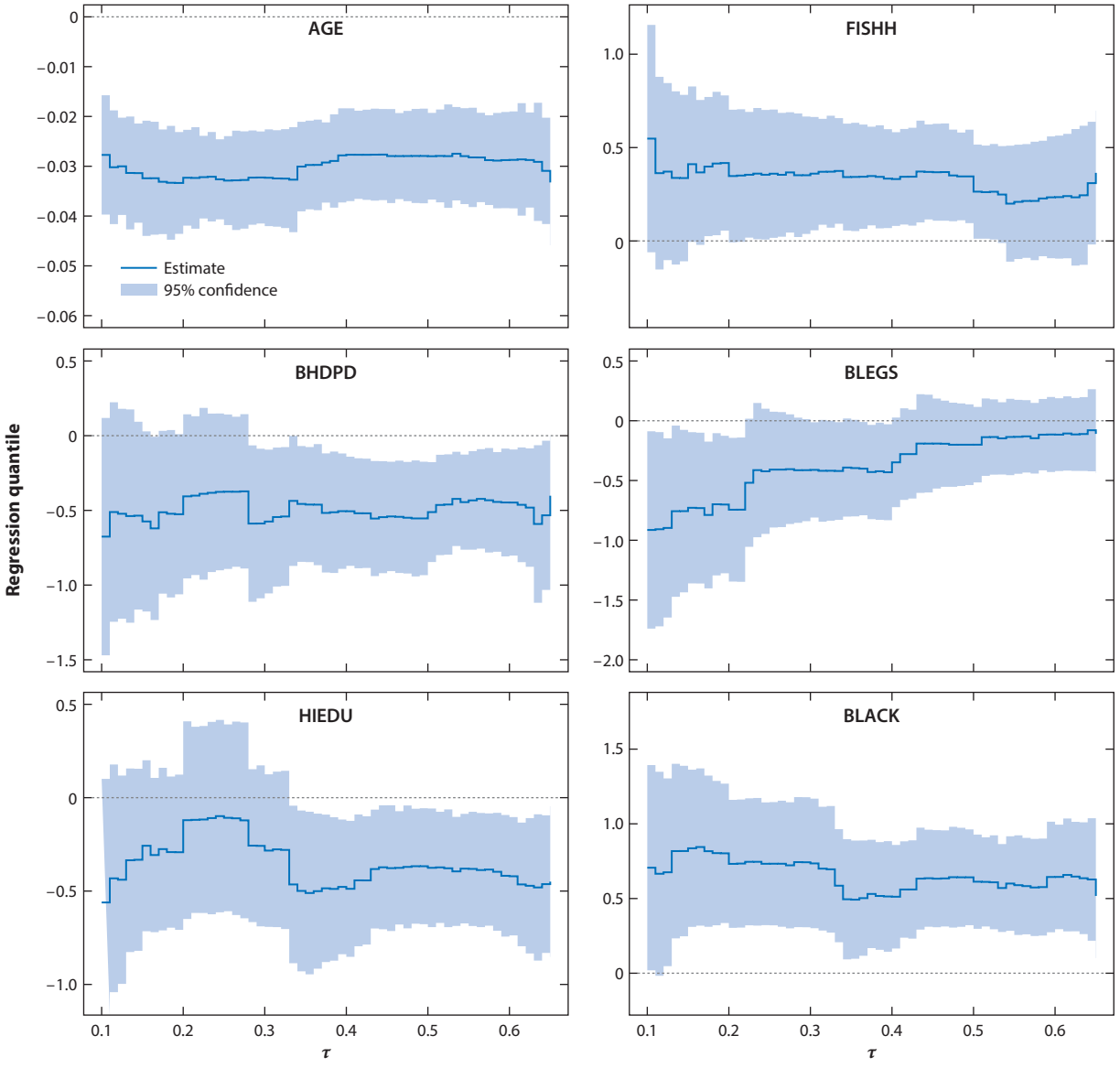

Figure 2

The dialysis example: Peng & Huang's (2008) estimator (*dark blue lines*) and 95% pointwise confidence intervals (*light blue fields*) of regression quantiles. Adapted with permission from Peng & Huang (2008), figure 2. Abbreviations: AGE, patient age; BHDPD, indicator of baseline hemodialysis dialysis modality; BLACK, indicator of being black; BLEGS, binary variable indicating moderate to severe RLS symptoms versus mild RLS symptoms; FISHH, indicator of fish consumption over the first year of dialysis; HIEDU, indicator of education equal to or higher than college; RLS, restless leg syndrome.

implication that BLEGS may affect the survival experience of dialysis patients with short survival times but may have little impact on that of long-term survivors. The confirmed nonconstancy of the BLEGS coefficients further indicates the lack of fit of an AFT model for this dialysis data.

Table 2 Estimation of average covariate effects based on quantile regression

	Average effect	SE	*p*-Value
AGE	−0.030	0.003	<0.001
FISHH	0.327	0.116	0.005
BHDPD	−0.489	0.162	0.003
BLEGS	−0.369	0.161	0.022
HIEDU	−0.350	0.137	0.011
BLACK	0.654	0.144	<0.001

Abbreviation: AGE, patient age; BHDPD, indicator of baseline hemodialysis dialysis modality; BLACK, indicator of being black; BLEGS, binary variable indicating moderate to severe RLS symptoms versus mild RLS symptoms; FISHH, indicator of fish consumption over the first year of dialysis; HIEDU, indicator of education equal to or higher than college; SE, standard error.

We also estimate the average quantile effects defined as $\int_l^u \beta_0^{(i)}(u)\mathrm{d}u$ $(i = 2, \ldots, 7)$. The results are given in **Table 2**. We observe that the estimated average effect of BLEGS based on quantile regression has a larger magnitude compared with that based on the AFT model. The associated *p*-value is less than 0.05, providing some evidence for the association between RLS and dialysis survival. This example suggests that naively treating varying effects as constant ones may lead to attenuated covariate effect estimates and consequently result in biased conclusions.

5.2. An Example of Quantile Regression Analysis with Competing Risks Data

We use the data set from the breast cancer trial E1178 by the Eastern Cooperative Oncology Group (Cummings et al. 1993). In this study, patient follow-up continued until breast cancer recurrence (BCR) or nonrecurrence related death (NRD), whichever occurred first. This data set includes 82 patients assigned to placebo and 85 patients assigned to tamoxifen. In the tamoxifen group, 42 patients experienced BCR and 23 died without recurrence; in the placebo group, 59 patients had BCR and 19 died without recurrence.

We apply the quantile regression strategy to evaluate the difference between two-year tamoxifen therapy versus placebo, while adjusting for other potential risk factors, including age, tumor size, and number of positive nodes. Since it is more clinically relevant to evaluate BCR in the presence of NRD than with the unrealistic exclusion of NRD, we choose to use the cumulative incidence quantile regression method (Peng & Fine 2009) to analyze this competing risks data set.

Figure 3 shows the BCR and NRD cumulative incidence functions separately for patient groups stratified by treatment and by age, number of positive nodes, and tumor size dichotomized at their median values, which are 71 years, 3 nodes, and 25 mm, respectively. From **Figure 3**, we observe that all BCR cumulative incidence curves exceed 0.45 in the right tails. In contrast, the cumulative incidence curves for NRD are below 0.20. A visual impression from **Figure 3** is that tamoxifen, number of positive nodes, and tumor size may impact the cumulative incidence of BCR but not NRD, and their effects on BCR may not be constant.

We apply Peng & Fine's (2009) method to fit the data with the competing risks quantile regression model, Equation 13, where the failure type corresponds to BCR and the exponential link function is replaced by the identify function. The number of positive nodes is incorporated into the model after log-transformation. Based on the results in **Figure 3**, we let $[\tau_L, \tau_U] = [0.10, 0.45]$. The analysis results displayed in **Figure 4** suggest that patients who received a placebo tend to experience BCR sooner than those on tamoxifen. In this example, age does not show a significant effect on the timing of BCR in the presence of nonrecurrence death. The effects of tumor size and number of positive nodes demonstrate an interesting increasing trend. The

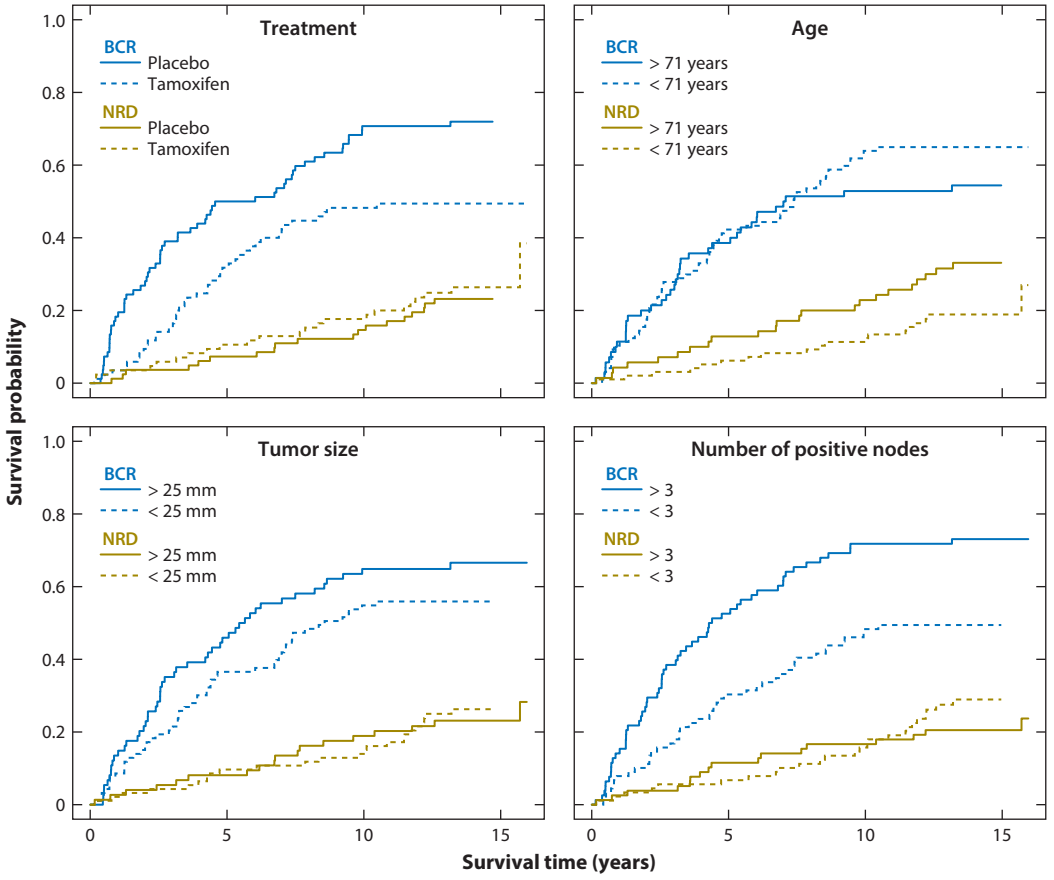

Figure 3

E1178 breast cancer trial example: estimated cumulative incidence functions. Adapted with permission from Peng & Fine (2009), figure 1. Abbreviations: BCR, breast cancer recurrence; NRD, nonrecurrence related death.

coefficient estimates, coupled with the 95% confidence intervals, suggest that tumor size and positive node number may only have a significant influence on the BCR cumulative incidence quantiles with relatively larger τs, such as $\tau = 0.35$ or 0.4. The changing trend of the effects of tumor size and node number over τ is confirmed by second-stage constancy tests. The clinical implication may be that either tumor size or number of positive nodes may significantly shorten the time to BCR for patients with moderate or low risk of BCR (corresponding to large τs), while such an impact may vanish when patients are subject to high risk of BCR (corresponding to small τs), possibly due to worse preexisting health condition or other unknown factors. The treatment coefficients are rather constant and are significantly above zero for many τs. This reflects the beneficial effect of tamoxifen treatment in terms of prolonging the progression to BCR.

6. REMARKS

Applying quantile regression to analyze survival data can provide robust and dynamic insight about the association between covariates and survival outcomes, which may not be offered by traditional survival regression methods. There have been rich developments in quantile regression methods for survival data in the past two decades. In this article, we provide a selective review of approaches

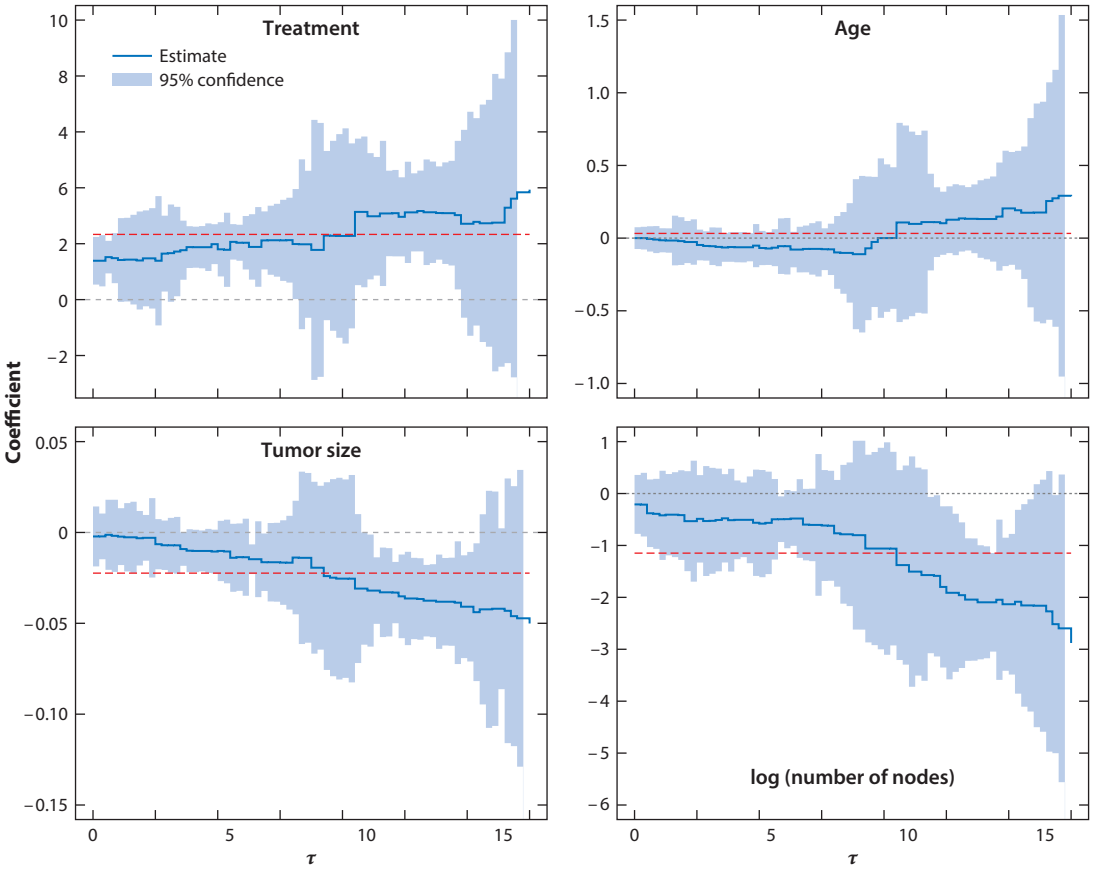

Figure 4

E1178 trial example: estimated regression coefficients for the breast cancer recurrence endpoint. Dark blue lines represent coefficient estimates, light blue fields represent 95% pointwise confidence intervals, and dashed red lines represent estimates for trimmed mean covariate effects. Adapted with permission from Peng & Fine (2009), figure 2.

available to handle various types of survival data, including randomly censored data, competing and semicompeting risks data, truncated data, and recurrent events data. Most of these methods are easy and stable to implement. This feature can help foster the applications of quantile regression in survival analysis.

Due to space limitations, we omit many important relevant method developments. These include, but are not limited to, cure rate quantile regression methods (Wu & Yin 2013, 2017a,b) and censored quantile regression methods attending to regression quantile monotonicity across quantile levels, such as semiparametric copula quantile regression (De Backer et al. 2017).

Some important problems not covered in this article but worth attention are quantile regression for survival data with high-dimensional covariates, survival data with time-dependent covariates, and survival data with missing covariates. This article also does not discuss scenarios where the collection of survival data is attached to a special epidemiologic design, such as case-cohort design and nested case-cohort design. Another interesting direction for extending survival quantile regression is to integrate quantile regression with causal inference. Work has emerged along these directions and merits further research efforts.

DISCLOSURE STATEMENT

The author is not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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Errata

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