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Quantile association regression on bivariate survival data

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Abstract: The association between two event times is of scientific importance in various fields. Due to population heterogeneity, it is desirable to examine the degree to which local association depends on different characteristics of the population. Here we adopt a novel quantile-based local association measure and propose a conditional quantile association regression model to allow covariate effects on local association of two survival times. Estimating equations for the quantile association coefficients are constructed based on the relationship between this quantile association measure and the conditional copula. Asymptotic properties for the resulting estimators are rigorously derived, and induced smoothing is used to obtain the covariance matrix. Through simulations we demonstrate the good practical performance of the proposed inference procedures. An application to age-related macular degeneration (AMD) data reals interesting varying effects of the baseline AMD severity score on the local association between two AMD progression times. *The Canadian Journal of Statistics* 00: 000–000; 2020 © 2020 Statistical Society of Canada

Résumé: L'association entre les temps jusqu'à deux événements revêt une importance scientifique dans plusieurs domaines. Il est intéressant de pouvoir observer à quel point leur degré d'association local dépend de différentes caractéristiques d'une population lorsque celle-ci exhibe de l'hétérogénéité. Les auteures adoptent une nouvelle mesure d'association locale basée sur les quantiles et proposent un modèle conditionnel de régression quantile permettant aux covariables d'avoir un effet sur l'association locale de deux temps de survie. Elles construisent les équations d'estimation pour les coefficients du modèle à partir de la relation entre cette mesure d'association quantile et la copule conditionnelle. Elles dérivent rigoureusement les propriétés asymptotiques des estimateurs résultants et utilisent un lissage induit afin d'obtenir la matrice de covariance. À l'aide de simulations, les auteures démontrent les bonne performances pratiques des procédures d'inférence proposées. Elles présentent une application à des données de dégénérescence maculaire liées à l'âge (DMA) qui montrent des effets variables du score de sévérité de base de la DMA sur l'association locale entre deux temps de progression de la DMA. *La revue canadienne de statistique* 00: 000–000; 2020 © 2020 Société statistique du Canada

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1. INTRODUCTION

The association between two failure times is often of interest in familial studies, finance and biomedical research. For example, in an atherosclerosis study, two diseases, myocardial infarction and stroke, are likely associated with each other. Understanding their association may help prevent the occurrence of one event, once the other event is observed. Another example is the bilateral eye disease age-related macular degeneration (AMD) which is a leading cause of vision loss in developed countries (Swaroop et al., 2009). A patient who was identified to have AMD in one eye may have a higher risk of AMD development or progression in the other eye.

Several global dependence measures have been developed to quantify the strength of association between pairs, including Kendall's tau (Oakes, 1982; 2008; Wang & Wells, 2000; Lakhal, Rivest & Beaudoin, 2009) and the correlation between two cumulative variates (Hsu & Prentice, 1996). Global association measures are appealing for their ease of interpretation. However, they cannot capture the local association structure which may vary over time. Research attention has been attracted to local association measures, which can effectively capture the association pattern in addition to the association strength. One approach to quantifying local association is to analyze the bivariate survival data via a frailty or copula framework (Clayton, 1978; Oakes, 1989; Shih & Louis, 1995; Romeo, Meyer & Gallardo, 2018), which allow time-dependent association between two failure times. Anderson et al., (1992) considered the time-dependent conditional expected residual life and conditional probability to quantify time-dependent association in bivariate survival data under the proportional hazard frailty model. Local association measures that relax the parametric copula or frailty assumptions include a martingale covariance function for two failure times (Prentice & Cai, 1992), a piecewise constant cross hazard ratio (Nan et al., 2006), and a time-dependent cross ratio (Hu & Nan, 2011), among others.

In the analysis of association, it is of interest to investigate how risk factors affect the local association between two event times. Conditional association tends to be more informative than their unconditional counterpart, because it can accommodate important risk factors and control for potential confounders. In the AMD example, age, genetic risk alleles and smoking status are possible risk factors for the development of AMD. They may also influence how the AMD progression times of the two eyes relate with one another for the same subject. By identifying those patients with stronger local association, clinicians can provide them earlier interventions once they show symptoms of AMD in one eye, to prevent or delay the development of AMD in the other eye. Earlier studies (Huster, Brookmeyer & Self, 1989; Gorfine, Zucker & Hsu, 2006; Zeng, Chen & Ibrahim, 2009) have focused on adjusting for covariate effects on marginal distributions, but not directly on the association. More recently, Bogaerts & Lesaffre (2008) and Geerdens, Acar & Janssen (2017) considered covariate-dependent conditional association by modelling covariate effects on parameters in a frailty or copula model. Yan & Fine (2005) proposed a functional association regression model on a temporal process with time-varying coefficient effects, though the temporal association may be affected by the assumed marginal distributions. Instead of focusing on copula parameters, Li et al., (2017) proposed an association model based on the odds ratio for quantiles, and considered the covariate effects on the marginal distributions only.

In this work, we propose a conditional association model for bivariate survival data, by adopting a novel quantile-specific association measure—the quantile odds ratio (*qor*) as proposed in Li, Cheng & Fine (2014). The *qor* is independent of the marginal distributions, invariant to monotone transformations, and insensitive to outliers. Li, Cheng & Fine (2014) utilized existing quantile regression models to allow covariate effects on marginal quantiles, and developed regression models for the *qor* for completely observed bivariate outcomes. For bivariate survival data, Li et al., (2017) successfully explored the quantile association through the *qor* in the copula framework, and proposed two estimators of the quantile association by

using non-parametric and semi-parametric methods, respectively. Although Li et al., (2017) considered the covariate effects in the estimation procedures, they assumed that covariate effects influence the quantile association via marginal quantiles only, which may be too restrictive in many real-life settings.

In this work, we propose a conditional quantile association model that allows covariate effects on both the marginal distributions and the association structure. This extension is a significant step forward in allowing direct covariate effects on the local association patterns. The modelling of covariate effects on quantile association is not trivial. The association is captured by a functional surface that is indexed by both quantiles, and both event times are subject to censoring. Meanwhile, we need to adjust for covariate effects on the marginals. To address these challenges, we adopt the flexible censored quantile regression model for marginal quantiles, and then propose a model to estimate the effects of the covariates on the conditional *qor*, through the relationship between *qor* and the conditional copula function. The estimation of covariance matrices is often tricky for quantile regression and quantile association analyses due to the unsmooth estimating equation. We thus extend an idea of the induced smoothing procedure (Brown & Wang, 2005) to explicitly estimate the influence functions for our proposed estimators, and propose an algorithm to obtain a consistent estimator for the covariance matrix of the proposed estimators. Our proposed method addresses the presence of right censoring and greatly expands the application of the method in Li, Cheng & Fine (2014) to time-to-event types of data.

The rest of this article is organized as follows. We propose our conditional quantile association model and estimating equations in Sections 2.1 and 2.2. The asymptotic properties for the coefficient estimators and the covariance estimation are given in Sections 2.3 and 2.4. We present numerical simulations for the proposed method and procedure in Section 3, and apply to an AMD study—age-related eye disease study (AREDS) in Section 4. Finally, some discussions are given in Section 5.

2. METHOD

2.1. Bivariate Survival Data and Models

To begin, we introduce necessary notation for bivariate survival data with covariates. Let (T_1, T_2) be a vector of bivariate survival times, and (C_1, C_2) be the corresponding vector of bivariate right censoring times. Define $Y_j = \min(T_j, C_j)$, $\delta_j = I(T_j \leq C_j)$, $j = 1, 2$. Let $\mathbf{Z}_j$ denote a vector of time-independent covariates that are relevant to T_j, $j = 1, 2$, and $\mathbf{Z}_j$ includes 1 as the first element. Let $\mathbf{Z}_3$ denote the covariate vector that is directly related to the association between the bivariate survival times. Define $\mathbf{Z}$ as a vector that consists all p covariates in $\mathbf{Z}_1$, $\mathbf{Z}_2$ and $\mathbf{Z}_3$. In the presence of independent censoring, the observed bivariate survival data consist of n i.i.d. replicates of $\{Y_{1i}, Y_{2i}, \delta_{1i}, \delta_{2i}, \mathbf{Z}_i\}_{i=1}^n$.

For $j = 1, 2$, define $F_j(t|\mathbf{Z}_j) = \Pr(T_j \leq t|\mathbf{Z}_j)$ as the marginal conditional cumulative distribution function (CDF) of T_j, and $Q_j(u|\mathbf{Z}_j) = \inf\{t : F_j(t|\mathbf{Z}_j) \geq u\}, u \in (0, 1)$ as the corresponding marginal conditional quantile function. Let $H(t_1, t_2|\mathbf{Z}) = \Pr(T_1 \leq t_1, T_2 \leq t_2|\mathbf{Z})$ be the conditional bivariate CDF of (T_1, T_2). The conditional copula function is defined as

$$C(\boldsymbol{\tau}|\mathbf{Z}) := \Pr\{T_1 \leq Q_1(\tau_1|\mathbf{Z}_1), T_2 \leq Q_2(\tau_2|\mathbf{Z}_2)|\mathbf{Z}\} = H\{Q_1(\tau_1|\mathbf{Z}_1), Q_2(\tau_2|\mathbf{Z}_2)|\mathbf{Z}\},$$

where $\boldsymbol{\tau} \equiv (\tau_1, \tau_2) \in (0, 1)^2$. To simplify the notation, we use $F_j(T_j|\mathbf{Z})$ to denote $F_j(T_j|\mathbf{Z}_j)$, for $j = 1, 2$, with the understanding that not all covariates in $\mathbf{Z}$ are significantly related to T_j or the conditional association. Thus, $H\{Q_1(\tau_1|\mathbf{Z}), Q_2(\tau_2|\mathbf{Z})|\mathbf{Z}\} \overset{d}{=} H\{Q_1(\tau_1|\mathbf{Z}_1), Q_2(\tau_2|\mathbf{Z}_2)|\mathbf{Z}\}$.

In this work we adopt a quantile association measure, quantile-specific odds ratio (*qor*), that was proposed by Li, Cheng & Fine (2014), where

$$\begin{aligned} qor(\boldsymbol{\tau}|\mathbf{Z}) &= \frac{\text{odds}\{T_1 \le Q_1(\tau_1|\mathbf{Z})|T_2 \le Q_2(\tau_2|\mathbf{Z})|\mathbf{Z}\}}{\text{odds}\{T_1 \le Q_1(\tau_1|\mathbf{Z})|T_2 > Q_2(\tau_2|\mathbf{Z})|\mathbf{Z}\}} \\ &= \frac{\text{odds}\{T_1 > Q_1(\tau_1|\mathbf{Z})|T_2 > Q_2(\tau_2|\mathbf{Z})|\mathbf{Z}\}}{\text{odds}\{T_1 > Q_1(\tau_1|\mathbf{Z})|T_2 \le Q_2(\tau_2|\mathbf{Z})|\mathbf{Z}\}} \\ &= \frac{\Pr\{T_1 \le Q_1(\tau_1|\mathbf{Z}), T_2 \le Q_2(\tau_2|\mathbf{Z})|\mathbf{Z}\} \times \Pr\{T_1 > Q_1(\tau_1|\mathbf{Z}), T_2 > Q_2(\tau_2|\mathbf{Z})|\mathbf{Z}\}}{\Pr\{T_1 \le Q_1(\tau_1|\mathbf{Z}), T_2 > Q_2(\tau_2|\mathbf{Z})|\mathbf{Z}\} \times \Pr\{T_1 > Q_1(\tau_1|\mathbf{Z}), T_2 \le Q_2(\tau_2|\mathbf{Z})|\mathbf{Z}\}}. \end{aligned} \tag{1}$$

The *qor* represents the odds that the first event occurs before (after) its quantile $Q_1(\tau_1|\mathbf{Z})$ given that the second event occurred before (after) its quantile $Q_2(\tau_2|\mathbf{Z})$, compared to the odds that the first event occurs before (after) its quantile $Q_1(\tau_1|\mathbf{Z})$ given that the second event occurred after (before) its quantile $Q_2(\tau_2|\mathbf{Z})$ (Li, Cheng & Fine, 2014; Li et al., 2017). Expressed as an odds ratio, the *qor* enjoys straightforward interpretation about the relationship between two event times. If there exists a positive (negative) association between T_1 and T_2, given the covariates, the *qor* is greater (less) than 1. If the two event times are conditionally independent, then the *qor* is equal to 1. Under different copula models, the *qor* changes with τ, except for the Plackett copula under which the *qor* stays constant; see Li, Cheng & Fine (2014) for more details.

It is easy to see that the $C(\boldsymbol{\tau}|\mathbf{Z})$ uniquely determines the *qor*. The opposite direction also holds true. Given that *qor*$= y$, by Equation (1), we have

$$\frac{C(\boldsymbol{\tau}|\mathbf{Z})\{1-\tau_1-\tau_2+C(\boldsymbol{\tau}|\mathbf{Z})\}}{\{\tau_1-C(\boldsymbol{\tau}|\mathbf{Z})\}\{\tau_2-C(\boldsymbol{\tau}|\mathbf{Z})\}} = y.$$

Because $0 < C(\boldsymbol{\tau}|\mathbf{Z}) < 1$, there is one unique solution for $C(\boldsymbol{\tau}|\mathbf{Z})$ as a function $\chi(y;\boldsymbol{\tau})$, where the form of χ depends on the value of y. Thus, we can express $C(\boldsymbol{\tau}|\mathbf{Z})$ as a function of the *qor*, $\chi\{qor(\boldsymbol{\tau}|\mathbf{Z});\boldsymbol{\tau}\}$, where

$$\chi(y;\boldsymbol{\tau}) := \begin{cases} \frac{\tau_1+\tau_2}{2} + \frac{1-\sqrt{(y-1)^2(\tau_1-\tau_2)^2+2(y-1)(\tau_1+\tau_2-2\tau_1\tau_2)+1}}{2(y-1)} & \text{if } 0 < y < 1 \text{ or } y > 1, \\ \tau_1\tau_2 & \text{if } y = 1, \end{cases}$$

$\lim_{y\to 0+}\chi(y;\boldsymbol{\tau}) = \max(0, \tau_1+\tau_2-1)$ and $\lim_{y\to\infty}\chi(y;\boldsymbol{\tau}) = \min(\tau_1,\tau_2)$. Thus, the conditional copula function has a monotone relationship with the *qor*.

We consider modelling covariate-dependent local association by positing that

$$\log qor(\boldsymbol{\tau}|\mathbf{Z}) = \mathbf{Z}^T\boldsymbol{\gamma}_0(\boldsymbol{\tau}), \tag{2}$$

where $\boldsymbol{\gamma}_0(\boldsymbol{\tau}) = \{\gamma_0^{(0)}(\boldsymbol{\tau}), \gamma_0^{(1)}(\boldsymbol{\tau}), \ldots, \gamma_0^{(p-1)}(\boldsymbol{\tau})\}$ is a $p \times 1$ vector of coefficients. $\gamma_0^{(0)}(\boldsymbol{\tau})$ corresponds to the baseline $\log qor(\cdot)$ when all covariates are set to zero. The absolute value of $\gamma_0^{(k)}(\boldsymbol{\tau})$ and the sign of $\gamma_0^{(k)}(\boldsymbol{\tau})$ represent the magnitude and the direction of the changes in the local association at the τth quantiles, when the kth covariate increases by one unit, with $k = 1, \ldots, p-1$, while other covariates stay constant. Under this structure, the conditional copula function has a form, $C(\boldsymbol{\tau}|\mathbf{Z}) = \chi[\exp\{\mathbf{Z}^T\boldsymbol{\gamma}_0(\boldsymbol{\tau})\};\boldsymbol{\tau}]$. Again in this article, we simply use the same $\mathbf{Z}$ for both marginal models and the local association model for notational brevity. In practice, different sets of covariates are allowed in models (2) and (3).

To model the $qor(\boldsymbol{\tau}|\mathbf{Z})$, it is necessary to have a sensible model for the marginal quantile functions, $Q_j(\tau_j|\mathbf{Z})$, $j = 1, 2$. To this end, we adopt the flexible and robust modelling framework of quantile regression (Koenker & Bassett, 1978). The framework is attractive in studying dynamic effects of covariates on an outcome, because it allows researchers to assess covariate effects across different quantiles of the outcome, and regression coefficients are easy to interpret. Quantile regression has been well extended to univariate survival data under different scenarios, such as survival data with independent censoring (Portnoy, 2003; Peng & Huang, 2008; Koenker, 2008), competing risks data (Peng & Fine, 2009) and left-truncated semi-competing risks data (Li & Peng, 2011), among others. Here, we adopt the censored quantile regression model (Portnoy, 2003; Peng & Huang, 2008; Koenker, 2008), which assumes that

$$Q_j(\tau_j|\mathbf{Z}) = g_j\{\mathbf{Z}^T\boldsymbol{\beta}_{j0}(\tau_j)\}, \tau_j \in (0, \tau_{U_j}), \tag{3}$$

where $\boldsymbol{\beta}_{j0}(\tau_j)$ is a $p \times 1$ vector of unknown coefficients, τ_{U_j} is the maximum quantile level that is estimable from the censored data and $g_j(\cdot)$ is a pre-specified monotone link function, for $j = 1, 2$. Common choices of $g_j(\cdot)$ include the identify link and the $\exp(\cdot)$ link. In the following, we adopt $g_j(\cdot) = \exp(\cdot)$, $j = 1, 2$, without loss of generality.

2.2. Estimating Equations

Before evaluating the association coefficients, $\boldsymbol{\gamma}_0(\boldsymbol{\tau})$, we need to first estimate the unknown parameters, $\boldsymbol{\beta}_{j0}(\tau_j)$, in the marginal censored quantile models. Without loss of generality, we adopt Peng & Fine (2009)'s method which uses inverse probability of censoring weighting (IPCW) to modify the standard quantile regression model in the estimation equation. More specifically, let $G_j(t|\mathbf{Z})$ be the survival function of C_j given $\mathbf{Z}$, $j = 1, 2$. The estimating equation for the true parameters, $\boldsymbol{\beta}_{j0}(\tau_j)$, is,

$$S_{nj}(\mathbf{b}_j; \tau_j) = n^{-1}\sum_{i=1}^{n}\mathbf{Z}_i\left[\frac{I\{Y_{ji} \le g_j(\mathbf{Z}^T\mathbf{b}_j)\}\delta_{ji}}{\widehat{G}_j(Y_{ji}|\mathbf{Z})} - \tau_j\right],$$

where $\widehat{G}_j(\cdot|\mathbf{Z})$ denotes a consistent estimator for G_j. For simplicity's sake, here we assume that C_j is independent of $(T_j, \delta_j, \mathbf{Z})$ and adopt the Kaplan–Meier estimator for $G_j(\cdot)$, $j = 1, 2$. When censoring depends on covariates, one can adopt some semi-parametric or non-parametric regression strategies to obtain $\widehat{G}_j(\cdot|\mathbf{Z})$. In practice, we focus on a pre-specified region of $\boldsymbol{\tau} \in \mathbb{D}$, where $\mathbb{D}$ is a subset of $(0, \tau_{U_1}] \times (0, \tau_{U_2}]$. Under mild regularity conditions, it has been shown that $S_{nj}(\mathbf{b}_j; \tau_j)$ is asymptotically mean zero at the true parameters $\boldsymbol{\beta}_{j0}$, and solving the estimating equation $S_{nj}(\mathbf{b}_j; \tau_j) = 0$ can be transformed into optimizing a L_1-type convex function. Therefore, despite that $S_{nj}(\mathbf{b}_j; \tau_j)$ is not smooth, the solution to $S_{nj}(\mathbf{b}_j; \tau_j) = 0$ can still be obtained by minimizing the L_1-type convex function (Peng & Fine, 2009). We use the existing software package, such as the *rq()* function in the R package *quantreq*, to obtain the estimators $\widehat{\boldsymbol{\beta}}_j(\tau_j)$ and the corresponding quantile estimators $\widehat{Q}_j(\tau_j|\mathbf{Z}) = g_j\{\mathbf{Z}^T\widehat{\boldsymbol{\beta}}_j(\tau_j)\}$ for $j = 1, 2$.

We now consider the main objective of this article of evaluating the quantile association effects, $\boldsymbol{\gamma}_0(\boldsymbol{\tau})$, with bivariate survival data. For complete data, it is easy to see that

$$E\{I(T_1 \le Q_1(\tau_1|\mathbf{Z}), T_2 \le Q_2(\tau_2|\mathbf{Z})|\mathbf{Z})\} = C(\boldsymbol{\tau}|\mathbf{Z}).$$

For bivariate survival data, we adapt a commonly used technique based on the IPCW to account for censoring. Under the assumption that the censoring times are conditionally independent of

(T_1, T_2) given $\mathbf{Z}$, we have

$$
\begin{aligned}
&E\left\{ \frac{I(Y_1 \le t_1, Y_2 \le t_2)\delta_1\delta_2}{G(Y_1, Y_2|\mathbf{Z})}\middle|\mathbf{Z}\right\} \\
&= E\left[E\left\{ \frac{I(T_1 \le t_1, T_2 \le t_2)I(T_1 \le C_1)I(T_2 \le C_2)}{G(Y_1, Y_2|\mathbf{Z})}\middle|T_1, T_2, \mathbf{Z}\right\}\middle|\mathbf{Z}\right] \\
&= E\left\{ \frac{I(T_1 \le t_1, T_2 \le t_2)G(T_1, T_2|\mathbf{Z})}{G(T_1, T_2|\mathbf{Z})}\middle|\mathbf{Z}\right\} \\
&= \Pr(T_1 \le t_1, T_2 \le t_2|\mathbf{Z}) = H(t_1, t_2|\mathbf{Z}),
\end{aligned}
$$

where $G(t_1, t_2|\mathbf{Z}) = \Pr(C_1 > t_1, C_2 > t_2|\mathbf{Z})$. Let $\widehat{G}(t_1, t_2|\mathbf{Z})$ be a consistent estimator of $G(t_1, t_2|\mathbf{Z})$. We can show that

$$
\begin{aligned}
E\left[\frac{I\{Y_1 \le Q_1(\tau_1|\mathbf{Z}), Y_2 \le Q_2(\tau_2|\mathbf{Z})\}\delta_1\delta_2}{\widehat{G}(Y_1, Y_2|\mathbf{Z})}\middle|\mathbf{Z}\right] &= \Pr(T_1 \le Q_1(\tau_1|\mathbf{Z}), T_2 \le Q_2(\tau_2|\mathbf{Z})|\mathbf{Z}) + o(1) \\
&= C(\boldsymbol{\tau}|\mathbf{Z}) + o(1) = \chi\{qor(\boldsymbol{\tau}|\mathbf{Z}), \boldsymbol{\tau}\} + o(1).
\end{aligned}
$$

Along with the consistent estimators of $Q_j(\tau_j|\mathbf{Z})$, $\widehat{Q}_j(\tau_j|\mathbf{Z})$, from the marginal quantile regression, and under the assumed conditional association effects model (2), we propose the following estimating function to estimate $\boldsymbol{\gamma}_0(\boldsymbol{\tau})$:

$$
\mathbf{W}_n^{\hat{G}}(\widehat{\boldsymbol{\beta}}_1, \widehat{\boldsymbol{\beta}}_2, \boldsymbol{\gamma}; \boldsymbol{\tau}) = \frac{1}{n}\sum_{i=1}^{n}\mathbf{Z}_i\left[\frac{I\{Y_{1i} \le \widehat{Q}_1(\tau_1|\mathbf{Z}), Y_{2i} \le \widehat{Q}_2(\tau_2|\mathbf{Z})\}\delta_{1i}\delta_{2i}}{\widehat{G}(Y_{1i}, Y_{2i}|\mathbf{Z})} - \chi\{\exp(\mathbf{Z}_i^T\boldsymbol{\gamma}); \boldsymbol{\tau}\}\right],
$$

where $\widehat{Q}_j(\tau_j|\mathbf{Z}) = g_j\{\mathbf{Z}^T\widehat{\boldsymbol{\beta}}_j(\tau_j)\}$ for $j = 1, 2$. For a fixed $\boldsymbol{\tau}$, $\mathbf{W}_n^{\hat{G}}(\widehat{\boldsymbol{\beta}}_1, \widehat{\boldsymbol{\beta}}_2, \boldsymbol{\gamma}; \boldsymbol{\tau})$ is smooth in $\boldsymbol{\gamma}$. Let $\chi'(\cdot; \boldsymbol{\tau})$ be the derivative of $\chi(\cdot; \boldsymbol{\tau})$. $\chi'(y, \boldsymbol{\tau})$ can be shown to be positive for $y \in \mathcal{R}$. Then,

$$
\partial\mathbf{W}_n^{\hat{G}}(\widehat{\boldsymbol{\beta}}_1, \widehat{\boldsymbol{\beta}}_2, \boldsymbol{\gamma}; \boldsymbol{\tau})/\partial\boldsymbol{\gamma} = -n^{-1}\sum_{i=1}^{n}\mathbf{Z}_i\mathbf{Z}_i^T\exp(\mathbf{Z}_i^T\boldsymbol{\gamma})\chi'\{\exp(\mathbf{Z}_i^T\boldsymbol{\gamma}); \boldsymbol{\tau}\}
$$

exists, and is a negative definite matrix. This ensures a unique solution to $\mathbf{W}_n^{\hat{G}}(\widehat{\boldsymbol{\beta}}_1, \widehat{\boldsymbol{\beta}}_2, \boldsymbol{\gamma}; \boldsymbol{\tau}) = 0$, which can be found by using the Newton–Ralphson algorithm which is implemented by the *multiroot()* function in the R package *rootSolve*.

There are a variety of methods to estimating $G(y_1, y_2|\mathbf{Z})$. To simplify the estimation, we assume that (C_1, C_2) are independent of $(T_1, T_2, \delta_1, \delta_2, \mathbf{Z})$ and use a consistent estimator for $G(y_1, y_2)$. In the AMD study and many similar applications, (T_1, T_2) represent correlated event times from the same participant, and the univariate censoring assumption is plausible. For such scenarios, we have $G(y_1, y_2) = \Pr\{C > \max(y_1, y_2)\}$, and one can adopt the Kaplan–Meier estimator on the basis of $\{\max(Y_{1i}, Y_{2i}), 1 - \delta_{1i}\delta_{2i}\}_{i=1}^n$. For more general bivariate censoring, consistent estimators such as the Prentice & Cai (1992) method can be used to estimate $G(y_1, y_2)$ on the basis of $\{Y_{1i}, 1 - \delta_{1i}, Y_{2i}, 1 - \delta_{2i}\}_{i=1}^n$.

2.3. Asymptotic Properties

In this subsection, we establish the uniform consistency and weak convergence of the proposed estimator $\widehat{\boldsymbol{\gamma}}_0(\boldsymbol{\tau})$ for $\boldsymbol{\tau} \in \mathbb{D}$. We first state some notation and the regularity conditions. For a vector $\mathbf{u}$, define $\mathbf{u}^{\otimes 2} = \mathbf{u}\mathbf{u}^T$ and $\|\mathbf{u}\|$ as its Euclidean norm. We use eigmin($\mathbf{A}$) to denote the minimal eigenvalue of a square matrix $\mathbf{A}$. Let $f_j(t|\mathbf{z}) = dF_j(t|\mathbf{z})/dt$, and $h_j(t_1, t_2|\mathbf{Z}) =$

$\partial H(t_1, t_2|\mathbf{Z})/\partial t_j$, for $j = 1, 2$. Let $\mathbf{A}_j(\mathbf{b}_j) = E[\mathbf{Z}^{\otimes 2} f_j\{g_j(\mathbf{Z}^T\mathbf{b}_j)|\mathbf{Z}\}]$ and $\mathbf{P}_j(\mathbf{b}_1, \mathbf{b}_2) = E[\mathbf{Z}^{\otimes 2} h_j\{g_1(\mathbf{Z}^T\mathbf{b}_1), g_2(\mathbf{Z}^T\mathbf{b}_2)|\mathbf{Z}\} g_j'(\mathbf{Z}^T\mathbf{b}_j)]$, where $g_j'(u) = dg_j(u)/du$. Denote $\mathbf{J}(\boldsymbol{\gamma}; \boldsymbol{\tau}) = E[\mathbf{Z}^{\otimes 2} \chi'\{\exp(\mathbf{Z}^T\boldsymbol{\gamma})\} \exp(\mathbf{Z}_i^T\boldsymbol{\gamma})]$, where $\chi'(u) = d\chi(u)/du$. The required regularity conditions are listed below:

C1. $\mathbf{Z}$ is uniformly bounded, that is, $\sup_i \|\mathbf{Z}_i\| < \infty$ for $i = 1, \ldots, n$.
C2. There exists $k_j > 0$ such that $\Pr(C_j = k_j) > 0$ and $\Pr(C_j > k_j) = 0$, for $j = 1, 2$. Moreover, there exists $\delta > 0$ such that $\Pr(C_1 \geq c_1, C_2 \geq c_2) > \delta > 0$ for any $c_j \leq k_j, j = 1, 2$.
C3. (i) $f_j(t|\mathbf{z})$ is bounded uniformly in t and $\mathbf{z}$, for $j = 1, 2$; (ii) $\boldsymbol{\beta}_{j0}(\tau_j)$ is Lipschitz continuous for τ_j, $j = 1, 2$, where $\tau = (\tau_1, \tau_2) \in \mathbb{D}$; (iii) there exists constants $\rho_b > 0$ and $k_b > 0$ such that $\inf_{\mathbf{b}_j \in \mathcal{B}_j(\rho_b)} \text{eigmin}\mathbf{A}_j(\mathbf{b}_j) > k_b$, where $\mathcal{B}_j(\rho_b) = \{\mathbf{b}_j \in R^p : \inf_{\boldsymbol{\tau} \in \mathbb{D}} \|\mathbf{b}_j - \boldsymbol{\beta}_{j0}(\tau_j)\| \leq \rho_b\}$, for $j = 1, 2$, $\boldsymbol{\tau} = (\tau_1, \tau_2)$; (iv) the copula function is differentiable with continuous partial derivatives with regard to τ_1 and τ_2 for any $\mathbf{Z}$.
C4. (i) $\boldsymbol{\gamma}_0(\boldsymbol{\tau})$ is Lipschitz continuous for $\boldsymbol{\tau} \in \mathbb{D}$; (ii) $\sup_{\boldsymbol{\tau} \in \mathbb{D}} \|\boldsymbol{\gamma}_0(\boldsymbol{\tau})\|$ is bounded above; (iii) there exists a constant $k_r > 0$ such that $\inf_{\tau \in \mathbb{D}} \text{eigmin}\{\mathbf{J}(\boldsymbol{\gamma}_0(\boldsymbol{\tau}); \boldsymbol{\tau})\} > k_r$.
C5. (i) For $j = 1, 2$, $f_j(t|\mathbf{z})$ are continuously differentiable with bounded derivatives; (ii) for $j = 1, 2$, $\partial h_j(t_1, t_2|\mathbf{Z})/\partial t_j$ are continuously differentiable with bounded derivatives.

Remarks: Condition C1 assumes the boundedness of covariates, and is often met in practice. Condition C2 is satisfied in many clinical settings with administrative censoring. Conditions C3 (i)–(iii) assume uniform boundedness of marginal densities and smoothness of coefficient processes, which are standard assumptions for marginal quantile regression methods with independent censoring data, and are usually reasonable in practice. Condition C3 (iv) implies the boundedness of $h_j(t_1, t_2|\mathbf{z})$ in (t_1, t_2) and $\mathbf{z}$. Condition C4 lists standard assumptions for quantile association models, including the boundedness of $\boldsymbol{\gamma}_0(\boldsymbol{\tau})$ and the identifiability of $\boldsymbol{\gamma}_0(\boldsymbol{\tau})$. Condition C5 contains mild assumptions for adopting a consistent covariance estimator.

Let $M_i^{G_j}(s) = I(Y_{ji} \leq s, \delta_{ji} = 0) - \int_0^\infty I(Y_{ji} \geq u) d\Lambda^{G_j}(u)$, where $\Lambda^{G_j}(u)$ is the cumulative hazard function for the censoring time C_j. Define

$$\xi_{1,ji}(\tau_j) = \mathbf{Z}_i\left(I\left[Y_{ji} \leq g\left\{\mathbf{Z}_i^T\boldsymbol{\beta}_{j0}(\tau_j)\right\}\right]\delta_{ji} G_j(Y_{ji})^{-1} - \tau_j\right), \text{ and}$$
$$\xi_{2,ji}(\tau_j) = \int_0^\infty w(\boldsymbol{\beta}_{j0}(\tau_j), s) P(Y_{ji} \geq s)^{-1} dM_i^{G_j}(s),$$

where $w\{\boldsymbol{\beta}_{j0}(\tau_j), s\} = E\{\mathbf{Z}I(Y_j \geq t)I[Y_j \leq g_j\{\mathbf{Z}^T\boldsymbol{\beta}_{j0}(\tau_j)\}]\delta_j G_j(Y_j)^{-1}\}$. Define $\xi_{ji}(\tau_j) = \xi_{1,ji}(\tau_j) - \xi_{2,ji}(\tau_j)$. To obtain the explicit form of the influence function, we here assume the univariate censoring mechanism. Let $Y_i^* = \max(Y_{1i}, Y_{2i})$ and $\delta_i^* = 1 - \delta_{1i}\delta_{2i}$. The univariate censoring function $G(\cdot)$ can be estimated from $\{Y_i^*, \delta_i^*\}_{i=1}^n$. Let $\hat{G}(\cdot)$ denote a consistent estimator of G. Define $N_i^G(t) = I(Y_i^* \leq t, \delta_i^* = 0)$ and $M_i^G(t) = N_i^G(t) - \int_0^\infty I(Y_i^* \geq s) d\Lambda^G(s)$, where Λ^G is the cumulative hazard function of G. Let

$$\xi_i^*(\boldsymbol{\tau}) = \int_0^\infty w^*\{\boldsymbol{\beta}_{10}(\tau_1), \boldsymbol{\beta}_{20}(\tau_2), s\} P(Y_i^* \geq s)^{-1} dM_i^G(s),$$

where $w^*\{\boldsymbol{\beta}_{10}(\tau_1), \boldsymbol{\beta}_{20}(\tau_2), s\} = E[\mathbf{Z}I\{g_1^{-1}(Y_1) \leq \mathbf{Z}^T\boldsymbol{\beta}_{10}(\tau_1), g_2^{-1}(Y_2) \leq \mathbf{Z}^T\boldsymbol{\beta}_{20}(\tau_2)\}\delta_1\delta_2 I(Y^* \geq s) G(Y^*)^{-1}]$.

Theorem 1. *Suppose models (2) and (3) hold for $\tau \in \mathbb{D}$. Under conditions C1–C5,* $\sup_{\boldsymbol{\tau} \in \mathbb{D}} \|\hat{\boldsymbol{\gamma}}(\boldsymbol{\tau}) - \boldsymbol{\gamma}_0(\boldsymbol{\tau})\| \xrightarrow{p} 0$.

Theorem 2. *Suppose models (2) and (3) hold for $\tau \in \mathbb{D}$. Under conditions C1–C5, $n^{1/2}\{\hat{\boldsymbol{\gamma}}(\boldsymbol{\tau}) - \boldsymbol{\gamma}_0(\boldsymbol{\tau})\}$ converges weakly to a zero-mean Gaussian process for $\tau \in \mathbb{D}$ with a limiting covariance matrix which equals*

$$\boldsymbol{\Omega}(\boldsymbol{\tau}', \boldsymbol{\tau}) = \mathbf{J}\{\boldsymbol{\gamma}_0(\boldsymbol{\tau}'); \boldsymbol{\tau}'\}^{-1} E\{\psi_i(\boldsymbol{\tau}')\psi_i(\boldsymbol{\tau})^T\}\mathbf{J}\{\boldsymbol{\gamma}_0(\boldsymbol{\tau}); \boldsymbol{\tau}\}^{-T},$$

where

$$\psi_i(\boldsymbol{\tau}) = \mathbf{Z}_i \frac{I\{g_1^{-1}(Y_{1i}) \le \mathbf{Z}_i^T \boldsymbol{\beta}_{10}(\tau_1), g_2^{-1}(Y_{2i}) \le \mathbf{Z}_i^T \boldsymbol{\beta}_{20}(\tau_2)\}\delta_{1i}\delta_{2i}}{G(Y_{1i}, Y_{2i})} - \xi_i^*(\boldsymbol{\tau})$$

$$- \mathbf{Z}_i \chi\{\exp(\mathbf{Z}_i^T \boldsymbol{\gamma}_0(\boldsymbol{\tau})); \boldsymbol{\tau}\} - \sum_{j=1}^{2} \mathbf{P}_j\{\boldsymbol{\beta}_{10}(\tau_1), \boldsymbol{\beta}_{20}(\tau_2)\}\mathbf{A}_j^{-1}\{\boldsymbol{\beta}_{j0}(\tau_j)\}\xi_{ji}(\tau_j). \quad (4)$$

The proofs for Theorems 1 and 2 are detailed in the Supplementary Material.

2.4. Covariance Estimation

The covariance estimation under quantile regression models is often challenging, because the asymptotic covariance matrix involves unknown conditional density functions. In previous studies, covariance estimation has been conducted using a kernel-based density estimator or resampling. These methods, however, do not extend well to the quantile association analysis Li, Cheng & Fine (2014). In this article, we employ the idea of the induced smoothing procedure that was proposed by Brown & Wang (2005) to estimate the covariance matrices for both marginal regression estimators and the conditional association coefficient estimators. The induced smoothing method smooths the original estimating equation by using a "pseudo-Bayesian" approach and has been successfully extended to the quantile regression setting (Brown & Wang, 2007; Wang, Shao & Zhu, 2009; Pang, Lu & Wang, 2012; Li, Cheng & Fine, 2014).

In the following, we first estimate the influence functions for the marginal regression estimators, and then further derive the influence function for the conditional association estimator. Without loss of generality, the univariate censoring scenario is considered to simplify the asymptotic representation. First, it has been shown in Peng & Fine (2009) that, under regularity conditions, $\sqrt{n}S_{nj}(\mathbf{b}_j, \tau_j)$ converges weakly to a mean-zero Gaussian process with covariance $\boldsymbol{\Sigma}_j(\tau_j', \tau_j) = \mathrm{cov}\{\xi_j(\tau_j)\}$ and the estimators, $\widehat{\boldsymbol{\beta}}_j(\tau_j)$, are consistent estimators of the true values $\boldsymbol{\beta}_{j0}(\tau_j)$. The asymptotic distribution for $n^{1/2}\{\widehat{\boldsymbol{\beta}}_j(\tau_j) - \boldsymbol{\beta}_{j0}(\tau_j)\}$ would be a mean-zero Gaussian process with covariance

$$\mathbf{D}_j(\boldsymbol{\beta}_{j0}; \tau_j) = \mathbf{A}_j\{\boldsymbol{\beta}_{j0}(\tau_j)\}^{-1}\boldsymbol{\Sigma}_j(\tau_j', \tau_j)\mathbf{A}_j\{\boldsymbol{\beta}_{j0}(\tau_j)\}^{-T},$$

where $\mathbf{A}_j(\mathbf{b}_j) = E[\mathbf{Z}^{\otimes 2} f_j\{g_j(\mathbf{Z}^T\mathbf{b}_j)\}] = \lim_{n\to\infty} n^{-1}\sum_{i=1}^{n} \mathbf{Z}_i^{\otimes 2} f_j\{g_j(\mathbf{Z}_i^T\mathbf{b}_j)\}$, for $j = 1, 2$.

We now adopt the induced smoothing approach to $S_{nj}(\mathbf{b}_j, \tau_j)$ and obtain a consistent estimator of $\mathbf{A}_j\{\boldsymbol{\beta}_{j0}(\tau_j)\}$. First, by the asymptotic normality of $\widehat{\boldsymbol{\beta}}_j(\tau_j)$, we can approximately write $\widehat{\boldsymbol{\beta}}_j(\tau_j) = \boldsymbol{\beta}_{j0}(\tau_j) + \mathbf{B}_j^{1/2} V_j$, where $\mathbf{B}_j = n^{-1}\mathbf{D}_j$, $V_j \sim N(0, I_p)$, and I_p is the $p \times p$ identity matrix. We can regard $\widehat{\boldsymbol{\beta}}_j(\tau_j)$ as a random perturbation of $\boldsymbol{\beta}_{j0}(\tau_j)$. Hence, we define a considerably smoother estimating function,

$$\tilde{S}_{nj}(\mathbf{b}_j, \mathbf{B}_j; \tau_j) = E_{V_j}\{S_{nj}(\mathbf{b}_j + \mathbf{B}_j^{1/2} V_j; \tau_j, \mathbf{B}_j)\}$$

$$= n^{-1}\sum_{i=1}^{n} \mathbf{Z}_i \left[\frac{\delta_{ji}}{\widehat{G}_j(Y_{ji})} \Phi\left\{ \frac{\mathbf{Z}_i^T\mathbf{b}_j - g_j^{-1}(Y_{ji})}{\sqrt{\mathbf{Z}_i^T\mathbf{B}_j\mathbf{Z}_i}} \right\} - \tau_j \right],$$

where $\Phi(\cdot)$ is the CDF of the standard normal distribution. Through the smoothed estimating function $\tilde{S}_{nj}(\mathbf{b}_j, \mathbf{B}_j; \tau_j)$, the estimator of $\mathbf{A}_j(\mathbf{b}_j)$ can be achieved from the derivative of the smoothed estimating equation with respect to $\mathbf{b}_j$, which has the form,

$$\tilde{\mathbf{A}}_j(\mathbf{b}_j, \mathbf{B}_j) = \frac{\partial \tilde{S}_{nj}(\mathbf{b}_j, \mathbf{B}_j; \tau_j)}{\partial \mathbf{b}_j} = n^{-1} \sum_{i=1}^{n} \frac{\delta_{ji} \mathbf{Z}_i^{\otimes 2}}{\widehat{G}_j(Y_{ji}) \sqrt{\mathbf{Z}_i^T \mathbf{B}_j \mathbf{Z}_i}} \phi\left\{ \frac{\mathbf{Z}_i^T \mathbf{b}_j - g_j^{-1}(Y_{ji})}{\sqrt{\mathbf{Z}_i^T \mathbf{B}_j \mathbf{Z}_i}} \right\}, \quad (5)$$

where $\phi(\cdot)$ is the probability density function of the standard normal distribution. Given $\mathbf{B}_j$, we can obtain the estimator $\tilde{\boldsymbol{\beta}}_j$ by solving $\tilde{S}_{nj}(\tilde{\boldsymbol{\beta}}_j, \mathbf{B}_j; \tau_j) = 0$ and then plug it into (5) to get the estimator,

$$\tilde{\mathbf{A}}_j(\tilde{\boldsymbol{\beta}}_j, \mathbf{B}_j) = n^{-1} \sum_{i=1}^{n} \frac{\delta_{ji} \mathbf{Z}_i^{\otimes 2}}{\widehat{G}_j(Y_{ji}) \sqrt{\mathbf{Z}_i^T \mathbf{B}_j \mathbf{Z}_i}} \phi\left\{ \frac{\mathbf{Z}_i^T \tilde{\boldsymbol{\beta}}_j - g_j^{-1}(Y_{ji})}{\sqrt{\mathbf{Z}_i^T \mathbf{B}_j \mathbf{Z}_i}} \right\}.$$

In general, the matrix $\mathbf{B}_j$ is unknown. Hence, we develop an iterative algorithm to achieve the optimal solutions for both $\boldsymbol{\beta}_{j0}(\tau_j)$ and $\mathbf{B}_j$. The detailed procedure is given below:

Step A0. Set the initial $\tilde{\mathbf{B}}_j^{(0)} = n^{-1} I_p$ and $\tilde{\boldsymbol{\beta}}_j^{(0)} = \widehat{\boldsymbol{\beta}}_j(\tau_j)$, and let $\widehat{\boldsymbol{\Sigma}}_j(\tau_j', \tau_j) = n^{-1} \sum_{i=1}^{n} \hat{\xi}_{ji}^{\otimes 2}$.

Step A1. In the kth iteration, update $\tilde{\boldsymbol{\beta}}_j^{(k)}$ by solving $\tilde{S}_n(\tilde{\boldsymbol{\beta}}_j^{(k-1)}, \tilde{\mathbf{B}}_j^{(k-1)}; \tau_j) = 0$.

Step A2. Update $\tilde{\mathbf{B}}_j^{(k)} = n^{-1}(\tilde{\mathbf{A}}_j^{(k)})^{-1} \widehat{\boldsymbol{\Sigma}}_j(\tau_j', \tau_j)(\tilde{\mathbf{A}}_j^{(k)})^{-T}$, where

$$\tilde{\mathbf{A}}_j^{(k)} = n^{-1} \sum_{i=1}^{n} \frac{\delta_{ji} \mathbf{Z}_i^{\otimes 2}}{\widehat{G}_j(Y_{ji}) \sqrt{\mathbf{Z}_i^T \tilde{\mathbf{B}}_j^{(k-1)} \mathbf{Z}_i}} \phi\left\{ \frac{\mathbf{Z}_i^T \tilde{\boldsymbol{\beta}}_j^{(k)} - g_j^{-1}(Y_{ji})}{\sqrt{\mathbf{Z}_i^T \tilde{\mathbf{B}}_j^{(k-1)} \mathbf{Z}_i}} \right\}.$$

Step A3. Repeat Steps A1–A2 until convergence.

This algorithm is computationally efficient and leads to a consistent covariance estimator $\tilde{\mathbf{D}}_j = n\tilde{\mathbf{B}}_j^{(k)}$ after the convergence of the iterations. More theoretical justifications and arguments were discussed in Pang, Lu & Wang (2012).

We next develop explicit estimators for the variance covariance matrix of $\widehat{\boldsymbol{\gamma}}(\boldsymbol{\tau})$. In Section 2.3, we have shown that the proposed asymptotic distribution of $\sqrt{n}\{\widehat{\boldsymbol{\gamma}}(\boldsymbol{\tau}) - \boldsymbol{\gamma}_0(\boldsymbol{\tau})\}$ is a mean-zero Gaussian process with covariance $\boldsymbol{\Omega}(\boldsymbol{\tau}', \boldsymbol{\tau}) = \mathbf{J}\{\boldsymbol{\gamma}_0(\boldsymbol{\tau}); \boldsymbol{\tau}\}^{-1} E\{\psi_i(\boldsymbol{\tau}')\psi_i(\boldsymbol{\tau})^T\} \mathbf{J}\{\boldsymbol{\gamma}_0(\boldsymbol{\tau}); \boldsymbol{\tau}\}^{-T}$. Define a consistent estimator of $\mathbf{J}\{\boldsymbol{\gamma}_0(\boldsymbol{\tau}); \boldsymbol{\tau}\}$ as

$$\widehat{\mathbf{J}}(\widehat{\boldsymbol{\gamma}}; \boldsymbol{\tau}) = n^{-1} \sum_{i=1}^{n} \mathbf{Z}_i^{\otimes 2} \chi'\{\exp(\mathbf{Z}_i^T \widehat{\boldsymbol{\gamma}})\} \exp(\mathbf{Z}_i^T \widehat{\boldsymbol{\gamma}}),$$

where $\chi'(u) = \partial \chi(u)/\partial u$. To have a consistent estimator for $E\{\psi_i(\boldsymbol{\tau}')\psi_i(\boldsymbol{\tau})^T\}$, we first estimate $\mathbf{P}_j\{\boldsymbol{\beta}_{10}(\tau_1), \boldsymbol{\beta}_{20}(\tau_2)\}$, where

$$\mathbf{P}_j\{\boldsymbol{\beta}_{10}(\tau_1), \boldsymbol{\beta}_{20}(\tau_2)\} = E\big(\mathbf{Z}^{\otimes 2} h_j[g_1\{\mathbf{Z}^T \boldsymbol{\beta}_{10}(\tau_1)\}, g_2\{\mathbf{Z}^T \boldsymbol{\beta}_{20}(\tau_2)\}] g_j'\{\mathbf{Z}^T \boldsymbol{\beta}_{j0}(\tau_j)\}\big).$$

However, estimating $\mathbf{P}_j\{\boldsymbol{\beta}_{10}(\tau_1), \boldsymbol{\beta}_{20}(\tau_2)\}$ directly is difficult since $\mathbf{P}_j(\cdot, \cdot)$ involves an unknown partial density function $h_j(\cdot, \cdot)$. To address this issue, we propose an induced-smoothing type estimator for $\mathbf{P}_j\{\boldsymbol{\beta}_{10}(\tau_1), \boldsymbol{\beta}_{20}(\tau_2)\}$, for $j = 1, 2$. For brevity, we simply the notation, such as

$\widehat{\boldsymbol{\beta}}_j = \widehat{\boldsymbol{\beta}}_j(\tau_j)$ and $\widehat{\boldsymbol{\gamma}} = \widehat{\boldsymbol{\gamma}}(\boldsymbol{\tau})$. Adapting the induced smoothing methods for the marginal quantile effects, we obtain a smoothed estimating function, where

$$\begin{aligned}\tilde{\mathbf{W}}_{nj}^{\hat{G}}(\mathbf{b}_j; \widehat{\boldsymbol{\beta}}_{j^*}, \widehat{\boldsymbol{\gamma}}, \widetilde{\mathbf{B}}_j) &= E_{V_j}\{\mathbf{W}_n^{\hat{G}}(\mathbf{b}_j + \widetilde{\mathbf{B}}_j^{1/2} V_j, \widehat{\boldsymbol{\beta}}_{j^*}, \widehat{\boldsymbol{\gamma}}; \boldsymbol{\tau})\} \\ &= n^{-1} \sum_{i=1}^{n} \mathbf{Z}_i \left[\frac{\delta_{1i}\delta_{2i} I\{g_{j^*}^{-1}(Y_{j^*i}) \le \mathbf{Z}_i^T \widehat{\boldsymbol{\beta}}_{j^*}\}}{\widehat{G}(Y_{1i}, Y_{2i})} \Phi\left\{ \frac{\mathbf{Z}_i^T \mathbf{b}_j - g_j^{-1}(Y_{ji})}{\sqrt{\mathbf{Z}_i^T \widetilde{\mathbf{B}}_j \mathbf{Z}_i}} \right\} - \chi\{\exp(\mathbf{Z}_i^T \widehat{\boldsymbol{\gamma}}); \boldsymbol{\tau}\} \right],\end{aligned}$$

where $\widetilde{\mathbf{B}}_j$ is the induced-smoothing type estimator for $\mathbf{B}_j$ from marginal quantile models, and $j^* = 3 - j$, for $j = 1, 2$. Therefore, $\mathbf{P}_j\{\boldsymbol{\beta}_{10}(\tau_1), \boldsymbol{\beta}_{20}(\tau_2)\}$ can be estimated by

$$\begin{aligned}\widehat{\mathbf{P}}_j^{\hat{G}}(\widehat{\boldsymbol{\beta}}_1, \widehat{\boldsymbol{\beta}}_2, \tilde{\mathbf{B}}_j) &= \left. \frac{\partial \tilde{\mathbf{W}}_{nj}^{\hat{G}}(\mathbf{b}_j; \widehat{\boldsymbol{\beta}}_{j^*}, \widehat{\boldsymbol{\gamma}}, \widetilde{\mathbf{B}}_j)}{\partial \mathbf{b}_j} \right|_{\mathbf{b}_j = \widehat{\boldsymbol{\beta}}_j} \\ &= n^{-1} \sum_{i=1}^{n} \frac{\mathbf{Z}_i^{\otimes 2} \delta_{1i}\delta_{2i} I\{g_{j^*}^{-1}(Y_{j^*i}) \le \mathbf{Z}_i^T \widehat{\boldsymbol{\beta}}_{j^*}\}}{\widehat{G}(Y_{1i}, Y_{2i}) \sqrt{\mathbf{Z}_i^T \widetilde{\mathbf{B}}_j \mathbf{Z}_i}} \phi\left\{ \frac{\mathbf{Z}_i^T \widehat{\boldsymbol{\beta}}_j - g_j^{-1}(Y_{ji})}{\sqrt{\mathbf{Z}_i^T \widetilde{\mathbf{B}}_j \mathbf{Z}_i}} \right\},\end{aligned}$$

where $j^* = 3 - j$, for $j = 1, 2$.

Combining these results, an algorithm for estimating the influence function $\psi_i(\boldsymbol{\tau})$ can be obtained by the following procedures:

Step A. For $j = 1, 2$, employ Steps A0–A3 in the aforementioned algorithm to assess $\widetilde{\mathbf{B}}_j$.
Step B. For $j = 1, 2$, let $j^* = 3 - j$ and define

$$\widehat{\mathbf{P}}_j^{\hat{G}}(\widehat{\boldsymbol{\beta}}_1, \widehat{\boldsymbol{\beta}}_2, \tilde{\mathbf{B}}_j) = n^{-1} \sum_{i=1}^{n} \frac{\mathbf{Z}_i^{\otimes 2} \delta_{1i}\delta_{2i} I\{g_{j^*}^{-1}(Y_{j^*i}) \le \mathbf{Z}_i^T \widehat{\boldsymbol{\beta}}_{j^*}\}}{\widehat{G}(Y_{1i}, Y_{2i}) \sqrt{\mathbf{Z}_i^T \widetilde{\mathbf{B}}_j \mathbf{Z}_i}} \phi\left\{ \frac{\mathbf{Z}_i^T \widehat{\boldsymbol{\beta}}_j - g_j^{-1}(Y_{ji})}{\sqrt{\mathbf{Z}_i^T \widetilde{\mathbf{B}}_j \mathbf{Z}_i}} \right\},$$

and

$$\widehat{\mathbf{A}}_j(\widehat{\boldsymbol{\beta}}_j) = n^{-1} \sum_{i=1}^{n} \frac{\delta_{ji} \mathbf{Z}_i^{\otimes 2}}{\widehat{G}_j(Y_{ji}) \sqrt{\mathbf{Z}_i^T \widetilde{\mathbf{B}}_j \mathbf{Z}_i}} \phi\left\{ \frac{\mathbf{Z}_i^T \widehat{\boldsymbol{\beta}}_j - g_j^{-1}(Y_{ji})}{\sqrt{\mathbf{Z}_i^T \widetilde{\mathbf{B}}_j \mathbf{Z}_i}} \right\}.$$

Step C. Plug in $\widehat{\boldsymbol{\beta}}_j$, $\widehat{\boldsymbol{\gamma}}$, $\widehat{\xi}_{ji}$, $\widehat{\xi}_i^*$, and the above estimates into (4). The resulting estimator for $\psi_i(\boldsymbol{\tau})$ is

$$\begin{aligned}\widehat{\psi}_i(\boldsymbol{\tau}) = \mathbf{Z}_i &\frac{I\{g_1^{-1}(Y_{1i}) \le \mathbf{Z}_i^T \widehat{\boldsymbol{\beta}}_1, g_2^{-1}(Y_{2i}) \le \mathbf{Z}_i^T \widehat{\boldsymbol{\beta}}_2\} \delta_{1i}\delta_{2i}}{\widehat{G}(Y_{1i}, Y_{2i})} - \mathbf{Z}_i \chi\{\exp(\mathbf{Z}_i^T \widehat{\boldsymbol{\gamma}}); \boldsymbol{\tau}\} \\ &- \widehat{\xi}_i^* - \sum_{j=1}^{2} \widehat{\mathbf{P}}_j\{\widehat{\boldsymbol{\beta}}_1, \widehat{\boldsymbol{\beta}}_2, \tilde{\mathbf{B}}_j\} \widehat{\mathbf{A}}_j^{-1}\{\widehat{\boldsymbol{\beta}}_j\} \widehat{\xi}_{ji}(\tau_j).\end{aligned}$$

By applying Steps A–C, we can further obtain an estimator for the covariance matrix,

$$\widehat{\boldsymbol{\Omega}}(\boldsymbol{\tau}', \boldsymbol{\tau}) = \widehat{\mathbf{J}}\{\widehat{\boldsymbol{\gamma}}; \boldsymbol{\tau}'\}^{-1} \left\{ n^{-1} \sum_{i=1}^{n} \widehat{\psi}_i(\boldsymbol{\tau}') \widehat{\psi}_i(\boldsymbol{\tau})^T \right\} \widehat{\mathbf{J}}\{\widehat{\boldsymbol{\gamma}}; \boldsymbol{\tau}\}^{-T},$$

where

$$\widehat{\mathbf{J}}(\widehat{\boldsymbol{\gamma}}; \boldsymbol{\tau}) = n^{-1} \sum_{i=1}^{n} \mathbf{Z}_i^{\otimes 2} \chi'\{\exp(\mathbf{Z}_i^T \widehat{\boldsymbol{\gamma}})\} \exp(\mathbf{Z}_i^T \widehat{\boldsymbol{\gamma}}),$$

which is a consistent estimator of $\mathbf{J}\{\widehat{\boldsymbol{\gamma}}; \boldsymbol{\tau}'\}$. Detailed justification for the consistency of $\widehat{\psi}_i(\boldsymbol{\tau})$ are provided in the Supplementary Material.

3. SIMULATION

In this section, numerical simulations are conducted to investigate the finite-sample performance of our proposed models. Without loss of generality, we focus on the case that $\tau_1 = \tau_2 = \tau$, as it has been shown in Li, Cheng & Fine (2014) that quantile association along the diagonal line can effectively depict the association structure. Two covariates are generated, Z_1 and Z_2, where Z_1 is a standard normal distributed variate and truncated at -2 and 2, and Z_2 is a Bernoulli distributed variate with probability 0.5. Denote $\mathbf{Z} = (Z_1, Z_2)$. For two event times T_1 and T_2, their marginal distributions follow the marginal quantile regression models with the exponential link function, $g_1(t) = g_2(t) = \exp(t)$, and

$$\log Q_1(\tau|\mathbf{Z}) = 0.2\Phi^{-1}(\tau) + 0.2Z_1 + \{0.4\Phi^{-1}(\tau) - 0.2\Phi^{-1}(\tau)\}Z_2,$$

$$\log Q_2(\tau|\mathbf{Z}) = 0.3\Phi^{-1}(\tau) - 0.2Z_1 + 0.5Z_2,$$

where $\Phi^{-1}(\cdot)$ is the inverse function of the CDF of the standard normal distribution. From the above models, the effect of Z_1 is constant across τ for both $\log Q_1(\tau|\mathbf{Z})$ and $\log Q_2(\tau|\mathbf{Z})$. The effect of Z_2 is constant on $\log Q_2(\tau|\mathbf{Z})$ but varies for $\log Q_1(\tau|\mathbf{Z})$ by τ.

To generate the association structure, we consider the situation that (T_1, T_2) follow a flipped-Clayton model with parameter θ when $Z_2 = 1$, and they are conditionally independent when $Z_2 = 0$. Specifically,

$$C(\boldsymbol{\tau}|Z_2 = 1) = \tau_1 + \tau_2 - 1 + \max[\{(1-\tau_1)^{-\theta} + (1-\tau_2)^{-\theta} - 1\}^{-1/\theta}, 0],$$

where $\theta = \exp(1)$. Thus, the underlying quantile association follows

$$\log qor(\boldsymbol{\tau}|\mathbf{Z}) = \log[\chi^{-1}\{C(\boldsymbol{\tau}|\mathbf{Z})\}]Z_2,$$

where $\chi^{-1}(y)$ is the inverse function of χ and is monotone increasing in y. Under this setting, the true value of $\boldsymbol{\gamma}_0(\boldsymbol{\tau})$ is $(0, 0, \log[\chi^{-1}\{C(\boldsymbol{\tau}|\mathbf{Z})\}])^T$, and Z_2 affects both the associational strength and structure.

For the censoring time, we consider the univariate censoring setting following the AMD data example, and generate C from a mixture distribution of Unif$(0, c_b)$ with probability 0.8, and a point mass at c_b with probability 0.2. Here, c_b mimics time to the end of a study in practical scenarios. The observed bivariate survival data are $(Y_1, Y_2, \delta_1, \delta_2, \mathbf{Z})$, where $Y_j = \min(T_j, C)$ and $\delta_j = I(Y_j \leq C)$, for $j = 1, 2$.

We performed 2,000 simulations with sample sizes $n = 200$ and 400. We set $c_b = 6$ or 4 so that the percentage of the censoring is about 20% or 30% respectively. For $\tau =$

0.2, 0.25, 0.3, 0.4, 0.5, 0.6, Table 1 presents the results of the empirical bias (Bias), the empirical standard error (Empse), the average estimated standard error (Estse) and the empirical coverage probability of 95% Wald-type confidence intervals (Cov) for (I) $\widehat{\boldsymbol{\beta}}_1(\tau)$, (II) $\widehat{\boldsymbol{\beta}}_2(\tau)$ and (III) $\widehat{\boldsymbol{\gamma}}(\boldsymbol{\tau})$, under 20% censoring rate. The results for 30% censoring are given in Table 2. From the top and middle parts of Table 1, we can see that, with 20% censoring rate, the estimated marginal quantile coefficients are largely unbiased across all τs; the induced smoothing standard errors agree well with the empirical ones, and the Wald-type confidence intervals based on the induced smoothing standard errors are close to the nominal level 95%. The results for the conditional association coefficients are shown in Table 1 (III) for 20% censoring. The biases for the association coefficients are larger than those for the marginal regression coefficients. This is as expected, since the estimation of covariate effects on the association structure is more challenging than the estimation of marginal effects. Nevertheless, the biases are largely negligible and shrink with the sample size, suggesting that the proposed estimator $\widehat{\boldsymbol{\gamma}}(\boldsymbol{\tau})$ provides accurate estimation of the true association effect across τs. The standard errors based on induced smoothing tend to be slightly larger than the empirical standard errors. Consequently, the coverage rates of Wald-type confidence intervals are greater than the nominal level 95% when $n = 200$. Li, Cheng & Fine (2014) also reported an inflated coverage rate of the confidence interval that was constructed based on the induced smoothing standard error for uncensored pairs. However, as the sample size increases, we observe that the coverage rates of Wald-type confidence intervals are closer to the nominal level 95%. This result implies that our proposed procedure performs adequately on the covariance estimation under moderate sample sizes. With 30% censoring rate, the results in Table 2 give similar conclusions as under 20% censoring rate, though the estimated standard deviations tend to be larger under 30% censoring than those under 20% censoring. We further conducted a simulation study with sample size $n = 600$ and censoring rate about 50% to mimic the AMD example. The results, given in Table 3 for $\tau = 0.15, 0.2, 0.25, 0.3, 0.35, 0.4$, present similar patterns as those under the previous scenarios. This result confirms the applicability of our methods to the AMD example.

4. DATA ANALYSIS

We illustrate our proposed methods by applying them to an AMD dataset from the AREDS (ARDES-Group, 1999), which was designed to examine the development and progression of AMD. This cohort study collected data on several risk factors at baseline, together with the progression times to late AMD in both eyes. The associational strength and pattern between the AMD progression times in two eyes reflect the prognostic value of one eye for the other eye and thereby have important implications in disease monitoring and treatment decision making. We aim to explore the explanatory factors for the underlying association using the proposed quantile-based association model, while adjusting for covariate effects on the marginals.

Data from 630 Caucasian patients who had at least one eye in moderated AMD stage but no eye in late AMD at baseline are used in the current analysis. The bivariate survival times are the progression times (from baseline, i.e., the enrollment time) to late AMD in the left and right eyes. By the definition of the *qor* in Equation (1), the association will stay the same if we switch the labels for T_1 and T_2. Thus, we simply treat the event time from the left eye as T_1, and that from the right eye as T_2. Three potential risk factors, age, smoking status (Never, Former and Current), and the baseline eye-level AMD severity score (SevereBL-L or SevereBL-R), are considered in the marginal models for AMD progression in the left or right eye. For the conditional association model, instead of including both eyes' AMD severity scores, we adopt the average of AMD severity scores (AvgSevereBL) in both eyes at baseline to avoid the collinearity issue. The censoring rates for the left and right eyes are 47% and 44%, respectively. Since each bivariate survival pair is from the same patient, the censoring mechanism follows univariate censoring in this application. The overall censoring rate for the univariate censoring is 56%. Due to the heavy

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TABLE 1: Simulation results for (I) marginal quantiles coefficients for the first subject event; (II) marginal quantiles coefficients for the second subject event; (III) covariate effects on the quantile association, with censoring rate 20%.

		(I) $\widehat{\boldsymbol{\beta}}_1(\tau) = (\widehat{\beta}_1^{(0)}(\tau), \widehat{\beta}_1^{(1)}(\tau), \widehat{\beta}_1^{(2)}(\tau))^T$														
		$\widehat{\beta}_1^{(0)}(\tau)$					$\widehat{\beta}_1^{(1)}(\tau)$					$\widehat{\beta}_1^{(2)}(\tau)$				
n	τ	True	Bias	Empse	Estse	Cov	True	Bias	Empse	Estse	Cov	True	Bias	Empse	Estse	Cov
200	0.2	−0.168	0.001	0.031	0.031	0.923	0.2	0	0.033	0.032	0.932	−0.168	0.005	0.068	0.067	0.936
	0.25	−0.135	0.001	0.030	0.029	0.927	0.2	−0.001	0.032	0.031	0.932	−0.135	0.004	0.065	0.064	0.930
	0.3	−0.105	0.001	0.029	0.029	0.935	0.2	0	0.032	0.030	0.930	−0.105	0.004	0.062	0.063	0.938
	0.4	−0.051	0	0.028	0.028	0.926	0.2	0	0.030	0.030	0.936	−0.051	0.003	0.062	0.061	0.931
	0.5	0	0	0.028	0.028	0.938	0.2	0	0.031	0.030	0.930	0	0.002	0.063	0.062	0.926
	0.6	0.051	0	0.029	0.030	0.943	0.2	0.001	0.032	0.032	0.935	0.051	0	0.066	0.065	0.928
400	0.2	−0.168	0.001	0.021	0.022	0.942	0.2	0.001	0.025	0.023	0.924	−0.168	0.004	0.047	0.047	0.942
	0.25	−0.135	0.001	0.020	0.021	0.943	0.2	0.001	0.023	0.022	0.928	−0.135	0.002	0.045	0.045	0.942
	0.3	−0.105	0.001	0.020	0.020	0.946	0.2	0	0.022	0.021	0.936	−0.105	0.003	0.044	0.044	0.938
	0.4	−0.051	0.001	0.020	0.020	0.940	0.2	0.001	0.021	0.021	0.936	−0.051	0.001	0.044	0.043	0.946
	0.5	0	0.001	0.019	0.020	0.942	0.2	0.001	0.022	0.021	0.942	0	0.001	0.044	0.044	0.940
	0.6	0.051	0	0.020	0.021	0.948	0.2	0	0.023	0.022	0.938	0.051	0.002	0.046	0.046	0.946

TABLE 1: Continued

		(II) $\widehat{\boldsymbol{\beta}}_2(\tau) = (\widehat{\beta}_2^{(0)}(\tau), \widehat{\beta}_2^{(1)}(\tau), \widehat{\beta}_2^{(2)}(\tau))^T$														
		$\widehat{\beta}_2^{(0)}(\tau)$					$\widehat{\beta}_2^{(1)}(\tau)$					$\widehat{\beta}_2^{(2)}(\tau)$				
n	τ	True	Bias	Empse	Estse	Cov	True	Bias	Empse	Estse	Cov	True	Bias	Empse	Estse	Cov
200	0.2	−0.252	0	0.046	0.045	0.921	−0.2	0	0.039	0.037	0.926	0.5	0.002	0.067	0.065	0.939
	0.25	−0.202	0	0.044	0.044	0.934	−0.2	0	0.038	0.036	0.922	0.5	0.001	0.063	0.063	0.948
	0.3	−0.157	0	0.043	0.043	0.923	−0.2	0	0.037	0.036	0.932	0.5	0.001	0.062	0.062	0.942
	0.4	−0.076	0.002	0.042	0.041	0.934	−0.2	0	0.036	0.035	0.937	0.5	0	0.060	0.061	0.938
	0.5	0	0.001	0.041	0.042	0.936	−0.2	0	0.036	0.036	0.933	0.5	0.001	0.061	0.062	0.946
	0.6	0.076	0.001	0.042	0.044	0.938	−0.2	0	0.038	0.037	0.932	0.5	0.001	0.064	0.066	0.950
400	0.2	−0.252	0	0.032	0.032	0.938	−0.2	−0.001	0.027	0.026	0.934	0.5	0.003	0.046	0.046	0.938
	0.25	−0.202	0	0.030	0.031	0.938	−0.2	0	0.026	0.025	0.932	0.5	0.003	0.044	0.045	0.946
	0.3	−0.157	0	0.029	0.030	0.946	−0.2	−0.001	0.026	0.025	0.934	0.5	0.003	0.043	0.044	0.943
	0.4	−0.076	0.001	0.029	0.029	0.936	−0.2	0	0.025	0.025	0.933	0.5	0.002	0.042	0.043	0.948
	0.5	0	0.001	0.030	0.030	0.940	−0.2	0	0.025	0.025	0.934	0.5	0.003	0.044	0.044	0.948
	0.6	0.076	0.001	0.030	0.031	0.948	−0.2	0	0.027	0.026	0.932	0.5	0.002	0.045	0.046	0.942

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TABLE 1: Continued

		(III) $\widehat{\boldsymbol{\gamma}}(\boldsymbol{\tau}) = (\widehat{\gamma}^{(0)}(\tau), \widehat{\gamma}^{(1)}(\tau), \widehat{\gamma}^{(2)}(\tau))^T$														
		$\widehat{\gamma}^{(0)}(\tau)$					$\widehat{\gamma}^{(1)}(\tau)$					$\widehat{\gamma}^{(2)}(\tau)$				
n	τ	True	Bias	Empse	Estse	Cov	True	Bias	Empse	Estse	Cov	True	Bias	Empse	Estse	Cov
200	0.2	0	−0.078	0.745	0.822	0.982	0	−0.025	0.661	0.655	0.992	1.850	0.122	1.037	1.112	0.976
	0.25	0	−0.015	0.606	0.657	0.974	0	−0.035	0.578	0.563	0.977	1.988	0.086	0.906	0.949	0.974
	0.3	0	0.015	0.542	0.574	0.972	0	−0.036	0.515	0.510	0.974	2.128	0.071	0.846	0.873	0.975
	0.4	0	0.059	0.468	0.500	0.972	0	−0.012	0.466	0.465	0.964	2.423	0.033	0.803	0.830	0.966
	0.5	0	0.074	0.461	0.495	0.967	0	−0.006	0.484	0.476	0.960	2.745	0.068	0.896	0.888	0.964
	0.6	0	0.062	0.531	0.558	0.963	0	−0.015	0.574	0.552	0.968	3.107	0.097	1.030	1.039	0.965
400	0.2	0	−0.046	0.516	0.530	0.979	0	−0.016	0.423	0.427	0.974	1.850	0.084	0.716	0.722	0.963
	0.25	0	−0.021	0.435	0.442	0.966	0	−0.013	0.378	0.377	0.958	1.988	0.062	0.625	0.635	0.963
	0.3	0	0.007	0.385	0.390	0.958	0	−0.016	0.339	0.345	0.962	2.128	0.037	0.577	0.590	0.958
	0.4	0	0.020	0.342	0.344	0.954	0	−0.008	0.315	0.318	0.952	2.423	0.034	0.563	0.566	0.954
	0.5	0	0.036	0.331	0.341	0.958	0	−0.009	0.321	0.324	0.958	2.745	0.019	0.588	0.595	0.958
	0.6	0	0.035	0.358	0.382	0.967	0	−0.009	0.372	0.370	0.953	3.107	0.042	0.672	0.683	0.960

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TABLE 2: Simulation results for (I) marginal quantiles coefficients for the first subject event; (II) marginal quantiles coefficients for the second subject event; (III) covariate effects on the quantile association, with censoring rate 30%.

		(I) $\widehat{\boldsymbol{\beta}}_1(\tau) = (\widehat{\beta}_1^{(0)}(\tau), \widehat{\beta}_1^{(1)}(\tau), \widehat{\beta}_1^{(2)}(\tau))^T$														
		$\widehat{\beta}_1^{(0)}(\tau)$					$\widehat{\beta}_1^{(1)}(\tau)$					$\widehat{\beta}_1^{(2)}(\tau)$				
n	τ	True	Bias	Empse	Estse	Cov	True	Bias	Empse	Estse	Cov	True	Bias	Empse	Estse	Cov
200	0.2	−0.168	0.001	0.033	0.032	0.938	0.2	0	0.034	0.034	0.926	−0.168	0.002	0.071	0.069	0.936
	0.25	−0.135	0.001	0.031	0.031	0.938	0.2	0.001	0.033	0.033	0.936	−0.135	0.001	0.067	0.067	0.938
	0.3	−0.105	0.001	0.030	0.030	0.934	0.2	0.001	0.032	0.032	0.936	−0.105	0.001	0.066	0.065	0.936
	0.4	−0.051	0.001	0.029	0.030	0.950	0.2	0.001	0.032	0.032	0.944	−0.051	0.002	0.066	0.065	0.930
	0.5	0	0.001	0.030	0.030	0.950	0.2	0.001	0.032	0.033	0.946	0	0.001	0.068	0.066	0.932
	0.6	0.051	0.001	0.031	0.032	0.948	0.2	0.001	0.034	0.035	0.952	0.051	0	0.071	0.070	0.942
400	0.2	−0.168	0.001	0.022	0.022	0.942	0.2	0.001	0.023	0.024	0.938	−0.168	0	0.050	0.049	0.938
	0.25	−0.135	0.001	0.021	0.022	0.948	0.2	0	0.022	0.023	0.948	−0.135	−0.001	0.048	0.047	0.930
	0.3	−0.105	0.001	0.020	0.021	0.949	0.2	0	0.021	0.022	0.952	−0.105	−0.001	0.047	0.046	0.926
	0.4	−0.051	0	0.020	0.021	0.944	0.2	0	0.022	0.022	0.944	−0.051	0	0.046	0.046	0.936
	0.5	0	0	0.021	0.021	0.946	0.2	0	0.022	0.023	0.943	0	0	0.047	0.047	0.942
	0.6	0.051	0	0.022	0.023	0.950	0.2	0.001	0.024	0.024	0.938	0.051	0.001	0.049	0.049	0.944

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TABLE 2: Continued

		(II) $\widehat{\boldsymbol{\beta}}_2(\tau) = (\widehat{\beta}_2^{(0)}(\tau), \widehat{\beta}_2^{(1)}(\tau), \widehat{\beta}_2^{(2)}(\tau))^T$														
		$\widehat{\beta}_2^{(0)}(\tau)$					$\widehat{\beta}_2^{(1)}(\tau)$					$\widehat{\beta}_2^{(2)}(\tau)$				
n	τ	True	Bias	Empse	Estse	Cov	True	Bias	Empse	Estse	Cov	True	Bias	Empse	Estse	Cov
200	0.2	−0.252	0.003	0.048	0.047	0.928	−0.2	−0.002	0.039	0.039	0.930	0.5	0.001	0.070	0.069	0.936
	0.25	−0.202	0.003	0.046	0.045	0.926	−0.2	−0.002	0.038	0.038	0.932	0.5	0.002	0.068	0.067	0.938
	0.3	−0.157	0.002	0.044	0.044	0.930	−0.2	−0.002	0.038	0.038	0.931	0.5	0.001	0.067	0.066	0.938
	0.4	−0.076	0.002	0.043	0.043	0.938	−0.2	−0.001	0.038	0.038	0.939	0.5	0.001	0.066	0.066	0.936
	0.5	0	0.002	0.044	0.044	0.928	−0.2	−0.001	0.038	0.039	0.939	0.5	0.001	0.067	0.068	0.934
	0.6	0.076	0.002	0.046	0.048	0.950	−0.2	−0.001	0.041	0.043	0.956	0.5	0	0.072	0.074	0.950
400	0.2	−0.252	0.001	0.033	0.033	0.934	−0.2	0.001	0.028	0.027	0.934	0.5	0.002	0.049	0.048	0.944
	0.25	−0.202	0.001	0.032	0.032	0.930	−0.2	0.001	0.027	0.026	0.935	0.5	0.001	0.047	0.047	0.943
	0.3	−0.157	0	0.032	0.031	0.932	−0.2	0	0.026	0.026	0.938	0.5	0.001	0.046	0.046	0.944
	0.4	−0.076	0	0.031	0.031	0.942	−0.2	0	0.026	0.026	0.941	0.5	0.001	0.045	0.046	0.940
	0.5	0	0.001	0.031	0.032	0.948	−0.2	0	0.027	0.027	0.944	0.5	0	0.046	0.048	0.949
	0.6	0.076	0.001	0.032	0.034	0.954	−0.2	0	0.029	0.030	0.956	0.5	0	0.049	0.052	0.958

TABLE 2: Continued

		(III) $\widehat{\boldsymbol{\gamma}}(\boldsymbol{\tau}) = (\widehat{\gamma}^{(0)}(\tau), \widehat{\gamma}^{(1)}(\tau), \widehat{\gamma}^{(2)}(\tau))^T$														
		$\widehat{\gamma}^{(0)}(\tau)$					$\widehat{\gamma}^{(1)}(\tau)$					$\widehat{\gamma}^{(2)}(\tau)$				
n	τ	True	Bias	Empse	Estse	Cov	True	Bias	Empse	Estse	Cov	True	Bias	Empse	Estse	Cov
200	0.2	0	−0.065	0.803	0.871	0.974	0	−0.020	0.725	0.724	0.996	1.850	0.148	1.118	1.191	0.976
	0.25	0	−0.039	0.663	0.698	0.978	0	−0.038	0.609	0.614	0.988	1.988	0.168	0.987	1.025	0.978
	0.3	0	−0.008	0.590	0.608	0.974	0	−0.030	0.564	0.558	0.979	2.128	0.130	0.915	0.949	0.976
	0.4	0	0.041	0.504	0.532	0.968	0	−0.026	0.517	0.513	0.964	2.423	0.099	0.896	0.918	0.970
	0.5	0	0.073	0.521	0.537	0.963	0	−0.028	0.554	0.533	0.955	2.745	0.081	0.980	1.001	0.968
	0.6	0	0.075	0.587	0.625	0.974	0	−0.026	0.635	0.637	0.980	3.107	0.134	1.167	1.229	0.976
400	0.2	0	−0.051	0.560	0.555	0.974	0	−0.006	0.437	0.454	0.980	1.850	0.082	0.747	0.763	0.966
	0.25	0	−0.012	0.449	0.462	0.970	0	−0.009	0.393	0.401	0.966	1.988	0.041	0.654	0.673	0.966
	0.3	0	0.011	0.389	0.409	0.964	0	0.002	0.360	0.370	0.961	2.128	0.030	0.616	0.631	0.954
	0.4	0	0.036	0.341	0.365	0.968	0	−0.003	0.332	0.346	0.956	2.423	0.026	0.606	0.615	0.956
	0.5	0	0.049	0.340	0.368	0.970	0	−0.005	0.347	0.359	0.959	2.745	0.025	0.640	0.660	0.960
	0.6	0	0.046	0.381	0.422	0.974	0	−0.001	0.410	0.418	0.960	3.107	0.020	0.748	0.775	0.969

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TABLE 3: Simulation results for (I) marginal quantiles coefficients for the first subject event; (II) marginal quantiles coefficients for the second subject event; (III) covariate effects on the quantile association, with sample size 600 and censoring rate 50%.

	(I) $\widehat{\boldsymbol{\beta}}_1(\tau) = (\widehat{\beta}_1^{(0)}(\tau), \widehat{\beta}_1^{(1)}(\tau), \widehat{\beta}_1^{(2)}(\tau))^T$														
	$\widehat{\beta}_1^{(0)}(\tau)$					$\widehat{\beta}_1^{(1)}(\tau)$					$\widehat{\beta}_1^{(2)}(\tau)$				
τ	True	Bias	Empse	Estse	Cov	True	Bias	Empse	Estse	Cov	True	Bias	Empse	Estse	Cov
0.15	−0.207	0.001	0.021	0.021	0.930	0.2	0	0.023	0.022	0.924	−0.207	0.002	0.044	0.044	0.938
0.2	−0.168	0.001	0.019	0.020	0.945	0.2	0	0.021	0.021	0.928	−0.168	0.001	0.041	0.042	0.950
0.25	−0.135	0.001	0.018	0.019	0.948	0.2	0	0.021	0.020	0.935	−0.135	0.001	0.040	0.041	0.942
0.3	−0.105	0.001	0.019	0.019	0.944	0.2	0	0.020	0.020	0.935	−0.105	0.001	0.040	0.040	0.942
0.35	−0.077	0.001	0.019	0.019	0.943	0.2	0	0.020	0.020	0.936	−0.077	0.001	0.040	0.040	0.945
0.4	−0.051	0.001	0.018	0.019	0.950	0.2	0	0.020	0.020	0.938	−0.051	0.001	0.040	0.040	0.938
	(II) $\widehat{\boldsymbol{\beta}}_2(\tau) = (\widehat{\beta}_2^{(0)}(\tau), \widehat{\beta}_2^{(1)}(\tau), \widehat{\beta}_2^{(2)}(\tau))^T$														
	$\widehat{\beta}_2^{(0)}(\tau)$					$\widehat{\beta}_2^{(1)}(\tau)$					$\widehat{\beta}_2^{(2)}(\tau)$				
τ	True	Bias	Empse	Estse	Cov	True	Bias	Empse	Estse	Cov	True	Bias	Empse	Estse	Cov
0.15	−0.311	0.001	0.030	0.030	0.938	−0.2	−0.001	0.027	0.026	0.924	0.5	0.002	0.046	0.046	0.944
0.2	−0.252	0.001	0.028	0.029	0.935	−0.2	−0.001	0.026	0.025	0.932	0.5	0.002	0.043	0.044	0.944
0.25	−0.202	0.001	0.027	0.028	0.940	−0.2	−0.001	0.025	0.024	0.934	0.5	0.002	0.042	0.043	0.942
0.3	−0.157	0.001	0.027	0.027	0.935	−0.2	−0.001	0.025	0.024	0.939	0.5	0.001	0.042	0.042	0.945
0.35	−0.116	0.002	0.027	0.027	0.937	−0.2	−0.001	0.025	0.025	0.940	0.5	0	0.042	0.043	0.948
0.4	−0.076	0.001	0.027	0.028	0.942	−0.2	−0.001	0.025	0.025	0.937	0.5	0.001	0.042	0.044	0.952

TABLE 3: Continued

	(III) $\widehat{\boldsymbol{\gamma}}(\boldsymbol{\tau}) = (\widehat{\gamma}^{(0)}(\tau), \widehat{\gamma}^{(1)}(\tau), \widehat{\gamma}^{(2)}(\tau))^T$														
	$\widehat{\gamma}^{(0)}(\tau)$					$\widehat{\gamma}^{(1)}(\tau)$					$\widehat{\gamma}^{(2)}(\tau)$				
τ	True	Bias	Empse	Estse	Cov	True	Bias	Empse	Estse	Cov	True	Bias	Empse	Estse	Cov
0.15	0	−0.081	0.585	0.620	0.982	0	-0.007	0.488	0.489	0.982	1.715	0.089	0.782	0.820	0.976
0.2	0	−0.027	0.454	0.474	0.972	0	-0.005	0.401	0.411	0.972	1.850	0.044	0.652	0.675	0.964
0.25	0	−0.008	0.385	0.402	0.972	0	-0.010	0.364	0.372	0.966	1.988	0.046	0.585	0.612	0.962
0.3	0	0.005	0.347	0.362	0.970	0	-0.008	0.341	0.349	0.969	2.128	0.046	0.566	0.584	0.964
0.35	0	0.017	0.324	0.339	0.962	0	-0.011	0.319	0.337	0.967	2.273	0.043	0.566	0.577	0.963
0.4	0	0.030	0.313	0.330	0.966	0	-0.012	0.322	0.335	0.962	2.423	0.031	0.576	0.588	0.958

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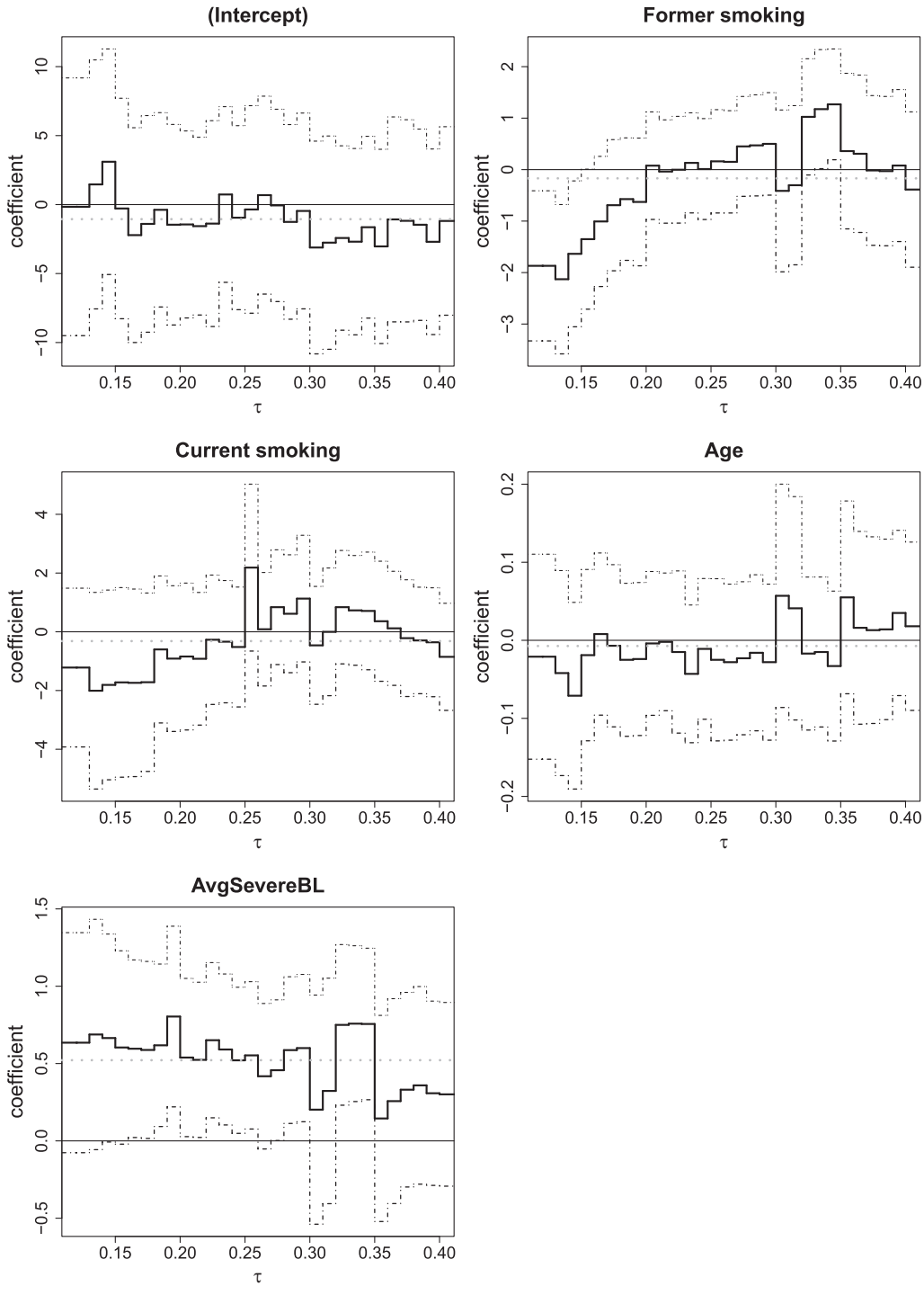

FIGURE 1: The estimated covariate effects on the association using the proposed model. The solid bold line is the estimated effect at each quantile level and the dotted line is the average across all levels. The dash-dot line is the 95% pointwise confidence interval.

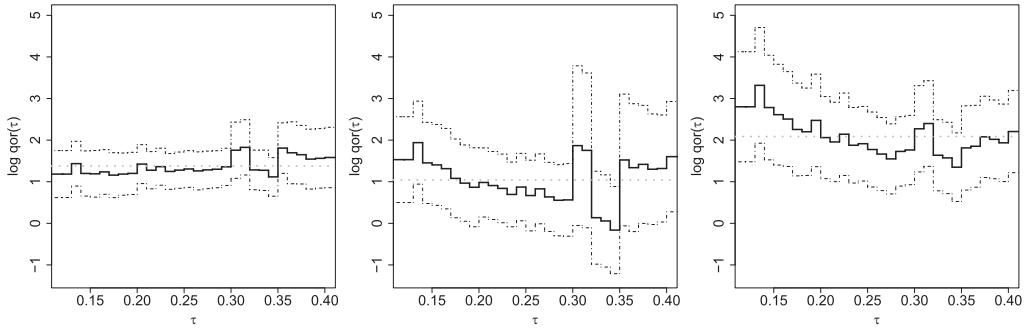

FIGURE 2: The log *qor* for two selected patients with different average baseline severity score (5 and 7 respectively). Both patients are non-smokers with 70 years of age. The left figure is the estimated log $qor(\boldsymbol{\tau})$ for the two patients using Li et al., (2017), which does not allow covariate effects on the local association. The middle and the right figures are the estimated log $qor(\boldsymbol{\tau}|\mathbf{Z})$ using the proposed method for the selected patients with average baseline severity score of 5 and 7, respectively.

censoring, we restrict attention to quantile levels up to 0.4. Meanwhile, due to sparse information at the boundary, there were some convergence issues at $\tau = 0.1$ for this data example. Thus, we select the lower limit 0.12 at which the estimation procedure converges.

The results for the marginal eyes are given in the Supplementary Material. For the marginal models, age and baseline severity score are mostly significant across quantiles, but the smoking status is only significant in a small range. The results for the conditional association model are shown in Figure 1. It suggests that the average AMD severity score has a significantly positive effect on the association at quantile level between 0.15 and 0.35. Moreover, the estimated coefficient for the average baseline AMD severity score is gradually decreasing but still positive, when the quantile increases. First, the positive coefficient implies that the odds of developing late AMD in one eye given the developed late AMD in the other eye is increasing, when the average baseline AMD severity score increases. Therefore, the associational strength between the progression times of the two eyes is stronger among those with higher AMD severity score at baseline. Next, the impact of the baseline average AMD severity score on the odds ratio is higher at short survival times (low quantiles) than at long survival times (high quantiles) while conditioning on age and smoking status. This suggests a varying effect of the baseline AMD severity score on the local association that cannot be captured by global association models. This result implies that, for a person who has a large average AMD severity score, if she/he suffers the development of late AMD in one eye in a short period, it is of importance to monitor the other eye as soon as possible.

In addition, we consider a benchmark analysis comparing our method and the one studied in Li et al., (2017). The marginal models in both approaches are the same. The major difference is that Li et al., (2017) only allowed covariate effects on the marginals, but did not allow covariate effects on the association structures. As our method detected significant associational effect of the severity score, the underlying assumption in Li et al., (2017) is likely not satisfied for this dataset. To see this, we selected two patients with different average severity scores at baseline, 5 and 7, but with the same age around the overall mean of 70 years and both non-smokers. We calculated the log *qor* for these two patients using our method and compared with the previous method. The results are given in Figure 2, where the left plot is the estimated log $qor(\boldsymbol{\tau})$ using the previous method as a benchmark analysis for both selected patients, and the middle and right figures are the log $qor(\boldsymbol{\tau}|\mathbf{Z})$ using our current method for each of the two selected patients. The

plots using our proposed method show that the patient with higher average of severity score at baseline exhibited stronger associations between two eyes across quantiles than the patient with lower severity score. This is completely missed by the benchmark analysis, as it forces everyone to have the same local association. Thus, additional insights are gained from directly modelling covariates to more accurately capture the association patterns over time or quantiles.

5. DISCUSSION

In this work, we propose a quantile-based regression model for the association between two event times with independent right censoring. The proposed quantile-based association regression model enables the evaluation of the strength of the local dependency between different quantiles of marginal survival times. More specifically, we use the idea of the copula to connect with the quantile-based local association *qor*, and estimate the coefficients for the association at different quantile levels. Our proposed model is very flexible, since it does not require any assumptions on the marginal distributions, and the form of the copula does not need to be specified either. We examine covariate effects on the quantile association directly while adjusting for risk factors in the marginal distributions. The estimated coefficients can be easily interpreted via the *qor*.

To have an explicit form of the asymptotic distribution, we assume the univariate censoring when evaluating the bivariate censoring function. In fact, the asymptotic distribution can still be established without the univariate censoring assumption. However it will not lead to a nice equation for the influence function, which has a consistent induced-smoothing type estimator. With the bivariate survival censoring, the covariance estimation can be achieved by using the bootstrap technique. However, it may result in a larger estimated standard deviation for the quantile type estimator, which is a common issue in the quantile approaches.

As Li, Cheng & Fine (2014) mentioned, the recommended range of quantiles for a study is associated with the sample size and the number of covariates. In our article for the bivariate survival data, the censoring rate also affects the range of quantiles, especially the upper bound level. Following Peng & Huang (2008), we recommend to choose the quantile range by taking into account the censoring rates and using an adaptive manner in practice. One may start by setting the lower range to 0.1 and the upper range to 1 minus the overall censoring rate. The range can be further adjusted if there are any signs of poor fit at the boundary of the quantile range, such as non-convergence or diverging standard error estimates. The restriction, in fact, is much accepted and universal in any quantile regression analyses of censored data.

We also notice through simulations (not reported here) that the strength of association in two event times may be affected by some residual covariate effects that have not been properly taken into account in the marginal models. Thus, we recommend considering all potential risk factors when evaluating the marginal distributions.

Finally, the dynamic association measurement is useful in capturing the local dependency. However, it would be desirable if we can connect our quantile association model with some commonly used global association measures, such as Kendall's tau. Some weighted local association across quantile levels may be considered. This will be a topic of future work.

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