A class of mean residual life regression models with censored survival data

LIUQUAN SUN

Institute of Applied Mathematics, Academy of Mathematics and Systems Science, Chinese Academy of Sciences, Beijing, 100080, P. R. China. *slq@amt.ac.cn*

QIANG ZHAO

Department of Mathematics

Texas State University, San Marcos, Texas, 78666, U.S.A. *qiang.zhao@txstate.edu*

Abstract

When describing a failure time distribution, the mean residual life is sometimes preferred to the survival or hazard rate. Regression analysis making use of the mean residual life function has recently drawn a great deal of attention. In this paper, a class of mean residual life regression models are proposed for censored data, and estimation procedures and a goodness-of-fit test are developed. Both asymptotic and finite sample properties of the proposed estimators are established, and the proposed methods are applied to a cancer data set from a clinic trial.

Keywords: Censored data; Estimating equation; Failure time; Goodness-of-fit test; Mean residual life.

Corresponding author: Liuquan Sun, Institute of Applied Mathematics, Academy of Mathematics and Systems Science, Chinese Academy of Sciences, Beijing 100080, P.R.China. E-mail: slq@amt.ac.cn.

1. INTRODUCTION

The mean residual life function (MRLF) is of interest in many fields such as reliability, survival analysis, actuarial studies, etc. For example, it is sometimes more informative to tell a prostate cancer patient how long he can survive or live without disease recurrence, in expectation, given his current situation (which of course includes the fact that he has "survived" or lived without the disease so far). As another example, a customer may be interested in knowing how much longer his or her computer can be used, given that the computer has worked normally for, say, t years. For a nonnegative survival time T with finite expectation, the MRLF at time $t \geq 0$ is

$$m(t) = E(T - t|T > t).$$

To assess the effects of covariates on the mean residual life, the proportional mean residual life model by Oakes and Dasu (1990) may be used:

$$m(t|Z) = m_0(t) \exp(\beta_0' Z), \tag{1}$$

where $m(t|Z)$ is the MRLF corresponding to the p-vector covariate Z, $m_0(t)$ is some unknown baseline MRLF when $Z = 0$, and β_0 is an unknown vector of regression parameters.

Previous work on the MRLF has focused on single-sample and two-sample cases (Oakes and Dasu, 1990). For regression analysis, Maguluri and Zhang (1994) used the underlying proportional hazards structure of the model to develop estimation procedures for β_0 in model (1), and Yuen, Zhu and Tang (2003) proposed a goodness-of-fit test for model (1), when there was no censoring involved. In the presence of censoring, Chen and Cheng (2005) used counting process theory to develop semiparametric inference procedures for β_0 in model (1), and Chen, et al. (2005) extended an estimation procedure of Maguluri and Zhang (1994) to censored survival data using inverse probability of censoring weighting techniques (Robins and Rotnitzky, 1992). Recently, Chen and Cheng (2006) and Chen (2007) proposed a new class of additive mean residual life model and discussed various estimation methodologies with or without right censoring. However, other regression forms may be more natural or descriptive in some applications.

In this paper, we consider a more general class of mean residual life regression models given by

$$m(t|Z) = m_0(t)g(\beta_0' Z), \tag{2}$$

where $g(t) \geq 0$ is pre-specified and assumed to be continuous almost everywhere and twice differentiable. Examples of possible link function include $g(x) = 1 + x$, $g(x) = e^x$ and $g(x) = \log(1 + e^x)$. Selection of an appropriate link function may be based on prior data or the resulting interpretation of the regression parameters.

In the next section, we will first discuss the situation where the censoring time is independent of T and Z, and a general inference procedure based on estimating functions is proposed. The procedure can be easily implemented numerically and the asymptotic properties of the proposed estimates of regression parameters are established. Section 3 generalizes the methods to the situation where the censoring time may depend on Z through the proportional hazards model. In Section 4, we develop test procedures for checking the adequacy of model (2) under both independent and dependent censoring scenarios based on an appropriate stochastic process which is asymptotically Gaussian. Section 5 reports some results from simulation studies conducted for evaluating the proposed methods. In Section 6, we apply the methodology to a data set from a cancer clinic trial and some concluding remarks are given in Section 7.

2. INFERENCE WITH INDEPENDENT CENSORING TIMES

In this section, let C be the potential censoring time, and assume that C is independent of T and Z. To avoid lengthy technical discussion of the tail behaviour of the limiting distributions, we further assume that $Pr\{C \geq \tau\} > 0$, where $0 < \tau = \inf\{t : Pr(T \geq t) = 0\} < \infty$. Let $\{T_i, C_i, Z_i\}$ $(i = 1, ..., n)$ be independent replicates of $\{T, C, Z\}$ and suppose that we observe $\{X_i, \delta_i, Z_i; i = 1, ..., n\}$, where $X_i = \min(T_i, C_i)$, $\delta_i = I(T_i \leq C_i)$. Here $I(\cdot)$ is the indicator function. Define

$$M_i(t) = N_i(t) - \int_0^t Y_i(u) d\Lambda(u|Z_i), \quad i = 1, ..., n, \tag{3}$$

where $N_i(t) = I(X_i \leq t, \delta_i = 1)$, $Y_i(t) = I(X_i \geq t)$, and $\Lambda(t|Z_i)$ is the cumulative hazard function of T_i given Z_i. It is well known that $M_i(t)$ $(i = 1, ..., n)$ are zero-mean martingale with respect to the σ-filtration $\sigma\{N_i(u), Y_i(u+), Z_i : 0 \leq u \leq t, i = 1, ..., n\}$.

Note that the survival function of T given Z is

$$S(t|Z) = \frac{m(0|Z)}{m(t|Z)} \exp\left\{-\int_0^t \frac{du}{m(u|Z)}\right\}.$$

Then under model (2), we have

$$m_0(t) d\Lambda(t|Z_i) = g(\beta_0' Z_i)^{-1} dt + dm_0(t). \tag{4}$$

Thus, in view of (3) and (4), for given β, a reasonable estimator for $m_0(t)$ is the solution to

$$\sum_{i=1}^n \left[m_0(t) dN_i(t) - Y_i(t)\left\{g(\beta' Z_i)^{-1} dt + dm_0(t)\right\}\right] = 0, \quad 0 \leq t \leq \tau. \tag{5}$$

Denote this estimator by $\hat{m}_{a0}(t; \beta)$. Straightforward algebra on (5) leads to

$$\hat{m}_{a0}(t; \beta) = \Phi_n(t)^{-1} \int_t^\tau \frac{\Phi_n(u) \sum_{i=1}^n Y_i(u) g(\beta' Z_i)^{-1}}{\sum_{i=1}^n Y_i(u)} du, \tag{6}$$

where $\Phi_n(t) = \exp\{-\int_0^t \sum_{i=1}^n dN_i(u) / \sum_{i=1}^n Y_i(u)\}$, which is the Nelson-Aalen estimator of the survival function for the pooled observations with independent censoring times. To estimate β_0, using the generalized estimating equation methods (Liang and Zeger, 1986; Cai and Schaubel, 2004; Chen and Cheng, 2005), we propose the following class of estimating equations for β_0,

$$\sum_{i=1}^n \int_0^\tau \frac{g^{(1)}(\beta' Z_i)}{g(\beta' Z_i)} Z_i \left[\hat{m}_{a0}(t; \beta) dN_i(t) - Y_i(t)\left\{g(\beta' Z_i)^{-1} dt + d\hat{m}_{a0}(t; \beta)\right\}\right] = 0,$$

where $g^{(1)}(x) = dg(x)/dx$. In view of (5), the above estimating equations are equivalent to

$$U_a(\beta) = n^{-1}\sum_{i=1}^{n}\int_0^{\tau}\left\{h(\beta' Z_i)Z_i - \bar{Z}_a(t;\beta)\right\}\left[\hat{m}_{a0}(t;\beta)dN_i(t) - Y_i(t)g(\beta' Z_i)^{-1}dt\right] = 0, \quad (7)$$

where $h(x) = g^{(1)}(x)/g(x)$, and

$$\bar{Z}_a(t;\beta) = \frac{\sum_{i=1}^{n} Y_i(t)h(\beta' Z_i)Z_i}{\sum_{i=1}^{n} Y_i(t)}.$$

Let $\hat{\beta}_a$ denote the solution to $U_a(\beta) = 0$ and $\hat{m}_{a0}(t) \equiv \hat{m}_{a0}(t;\hat{\beta}_a)$ the corresponding estimator of the unknown baseline mean residual life $m_0(t)$. Following the arguments of Chen and Cheng (2005) and Lin, Wei and Ying (2001), we can check that both $\hat{\beta}_a$ and $\hat{m}_{a0}(t)$ always exist and are unique and consistent. To study the asymptotic distribution of $\hat{\beta}_a$, we show in Appendix A.1 that $n^{1/2}U_a(\beta_0)$ is asymptotically normal with mean zero and covariance matrix that can be consistently estimated by $\hat{\Sigma}_a$, where

$$\hat{\Sigma}_a = n^{-1}\sum_{i=1}^{n}\int_0^{\tau}\left\{h(\hat{\beta}_a' Z_i)Z_i - \hat{\mu}(t)\right\}^{\otimes 2}\hat{m}_{a0}(t)^2 dN_i(t),$$

$$\hat{\mu}(t) = \bar{Z}_a(t;\hat{\beta}_a) + \frac{\Phi_n(t)}{\pi_n(t)}\int_0^t n^{-1}\sum_{i=1}^{n}\left[h(\hat{\beta}_a' Z_i)Z_i - \bar{Z}_a(u;\hat{\beta}_a)\right]\frac{dN_i(u)}{\Phi_n(u)},$$

and $\pi_n(t) = n^{-1}\sum_{i=1}^{n} Y_i(t)$. Here for a vector v, $v^{\otimes 0} = 1$, $v^{\otimes 1} = v$ and $v^{\otimes 2} = vv'$. Then it follows that $n^{1/2}(\hat{\beta}_a - \beta_0)$ is asymptotically normal with zero mean and covariance matrix that can be consistently estimated by $\hat{A}^{-1}\hat{\Sigma}_a\hat{A}^{-1}$, where

$$\hat{A} = n^{-1}\sum_{i=1}^{n}\int_0^{\tau}\left\{h(\hat{\beta}_a' Z_i)Z_i - \bar{Z}_a(t;\hat{\beta}_a)\right\}^{\otimes 2} Y_i(t)g(\hat{\beta}_a' Z_i)^{-1}dt.$$

We also show in Appendix A.2 that $n^{1/2}\{\hat{m}_{a0}(t) - m_0(t)\}$ $(0 \le t \le \tau)$ converges weakly to a zero-mean Gaussian process whose covariance function at (s,t) can be estimated consistently by $\hat{\Gamma}_a(s,t) = n^{-1}\sum_{i=1}^{n}\hat{\varphi}_i(s)\hat{\varphi}_i(t)$, where

$$\hat{\varphi}_i(t) = -\frac{1}{\Phi_n(t)}\int_t^{\tau}\frac{\Phi_n(u)}{\pi_n(u)}\left[\hat{m}_{a0}(u)dN_i(u) - Y_i(u)\left\{g(\hat{\beta}_a' Z_i)^{-1}du + d\hat{m}_{a0}(u)\right\}\right]$$

$$+\hat{m}_{a0}(t)\bar{Z}_a(t;\hat{\beta}_a)'\hat{A}^{-1}\int_0^{\tau}\left\{h(\hat{\beta}_a' Z_i)Z_i - \hat{\mu}(u)\right\}\left[\hat{m}_{a0}(u)dN_i(u)\right.$$

$$-Y_i(u)\big\{g(\hat{\beta}_a' Z_i)^{-1}du + d\hat{m}_{a0}(u)\big\}\Big].$$

The asymptotic normality for $\hat{m}_{a0}(t)$, together with the consistent variance estimator $\hat{\Gamma}_a(t,t)$, enables us to construct pointwise confidence intervals for $m_0(t)$. Since $m_0(t)$ is non-negative, one may want to use the log transformation for the construction of its confidence intervals. To construct simultaneous confidence bands for $m_0(t)$ over a time interval of interest $[t_1, t_2]$ $(0 < t_1 < t_2 \leq \tau)$, we need to evaluate the distribution of the supremum of a related process over $[t_1, t_2]$. It is not possible to evaluate such distributions analytically because the limiting process of $n^{1/2}\{\hat{m}_{a0}(t) - m_0(t)\}$ does not have an independent increments structure. To handle this problem, we use a resampling scheme to approximate the distribution of $n^{1/2}\{\hat{m}_{a0}(t) - m_0(t)\}$. Define

$$\widehat{W}_a(t) = n^{-1/2}\sum_{i=1}^{n}\hat{\varphi}_i(t)\Omega_i,$$

where $(\Omega_1, ..., \Omega_n)$ are independent standard normal variables which are independent of the data $\{X_i, \delta_i, Z_i; i = 1, ..., n\}$. According to the arguments of Lin et al. (2000), the distribution of the process $n^{1/2}\{\hat{m}_{a0}(t) - m_0(t)\}$ can be approximated by that of the zero-mean Gaussian process $\widehat{W}_a(t)$. To approximate the distributions of $n^{1/2}\{\hat{m}_{a0}(t) - m_0(t)\}$, we obtain a large number of realizations from $\widehat{W}_a(t)$ by repeatedly generating the normal random sample $(\Omega_1, ..., \Omega_n)$ while fixing the data $\{X_i, \delta_i, Z_i; i = 1, ..., n\}$ at their observed values. Using this simulation method, we may determine an approximate $1-\alpha$ simultaneous confidence bands for $m_0(t)$ over a time interval of interest $[t_1, t_2]$.

3. INFERENCE WITH DEPENDENT CENSORING TIMES

Now we consider the situation where T, C and Z may depend on each other, but given Z, we assume that T is independent of C. Also we assume that the hazard function of C given Z has the form

$$\lambda_c(t \mid Z) = \lambda_0(t)\exp\{\gamma_0' Z\}, \tag{8}$$

where $\lambda_0(t)$ is an unspecified baseline hazard function and γ_0 is a vector of unknown regression parameters. Note that the model from Section 2 is the model of Section 3 with $\gamma_0 = 0$. Of course, γ_0 is usually unknown. A natural estimate of γ_0, which is efficient under model (8), is given by the maximum partial likelihood estimate defined as the solution to

$$U_r(\gamma) \;=\; \sum_{i=1}^{n} \int_0^{\tau} \{Z_i - \bar{Z}_r(t;\gamma)\} dN_i^c(t) \;=\; 0 \tag{9}$$

(Cox, 1972), where $N_i^c(t) = I(X_i \le t, \delta_i = 0)$, and $\bar{Z}_r(t;\gamma) = S^{(1)}(t;\gamma)/S^{(0)}(t;\gamma)$, $S^{(k)}(t;\gamma) = \sum_{i=1}^{n} Y_i(t) Z_i^{\otimes k} \exp\{\gamma' Z_i\}$ for $k = 0, 1, 2$. Let $\hat{\gamma}$ denote the estimator given by $U_r(\gamma) = 0$, and $\hat{\Lambda}_0(t)$ be the Breslow estimator of $\Lambda_0(t) = \int_0^t \lambda_0(u) du$, where

$$\hat{\Lambda}_0(t) = \sum_{i=1}^{n} \int_0^t \frac{dN_i^c(u)}{\sum_{i=1}^{n} Y_i(u) \exp\{\hat{\gamma}' Z_i\}}.$$

Consider a hypothetical equilibrium renewal process formed by renewals following the same survival distribution as $S(t|Z)$. The forward recurrence time V is defined as the time from a fixed time to the next immediate renewal. Then under model (2), it follows from Cox (1962) that its hazard function is

$$\lambda_v(t|Z) = m(t|Z)^{-1} = m_0(t)^{-1} g(\beta_0' Z)^{-1},$$

which is a proportional hazards model. When there is no censoring, the following partial score equation can be used to estimate β_0 (Prentice and Self, 1983; Cai and Schaubel, 2004),

$$\hat{E}\{h(\beta' Z) Z\} - \int_0^{\tau} \frac{\hat{E}[h(\beta' Z) Z g(\beta' Z)^{-1} I(V \ge t)]}{\hat{E}[g(\beta' Z)^{-1} I(V \ge t)]} d\hat{F}_v(t) = 0, \tag{10}$$

where $\hat{E}$ and $\hat{F}_v(t)$ are their empirical estimates of the expectation E and $F_v(t)$, respectively. Here $F_v(t)$ is the distribution function of V. However, this equality is only theoretical, since we cannot observe V. To use the sample of T's in (10), following the arguments of Maguluri and Zhang (1994) and Cheng et al. (2005), we have that for any function $w(Z)$,

$$E\{w(Z) I(V \ge t)\} = m_0(0)^{-1} E\{w(Z) g(\beta_0' Z)^{-1} (T - t)^{+}\},$$

where $(T-t)^+$ denotes $(T-t)I(T \geq t)$. As a result,

$$dF_v(t) = \frac{E\{g(\beta_0'Z)^{-1}I(T>t)\}}{E\{g(\beta_0'Z)^{-1}T\}}dt.$$

Replacing the respective terms in (10), we obtain the following estimating equation for β based on T's,

$$n^{-1}\sum_{i=1}^{n} h(\beta' Z_i)Z_i - \int_0^{\tau} \frac{\sum_{i=1}^n h(\beta' Z_i)Z_i g(\beta' Z_i)^{-2}(T_i - t)^+}{\sum_{i=1}^n g(\beta' Z_i)^{-2}(T_i - t)^+} \frac{\sum_{i=1}^n g(\beta' Z_i)^{-1} I(T_i > t)}{\sum_{i=1}^n g(\beta' Z_i)^{-1} T_i} dt = 0. \tag{11}$$

Let $G_i(t;\gamma_0,\Lambda_0)$ be the censoring survival distribution of C_i given Z_i under model (8), that is, $G_i(t;\gamma_0,\Lambda_0) = \exp\big\{-\Lambda_0(t)\exp(\gamma_0' Z_i)\big\}$. Then for any well-defined function of ν,

$$E\left\{\frac{\nu(X_i,Z_i,t)\delta_i}{G_i(X_i;\gamma_0,\Lambda_0)}\right\} = E\left[E\left\{\frac{\nu(T_i,Z_i,t)\delta_i}{G_i(T_i;\gamma_0,\Lambda_0)}\Big| Z_i\right\}\right] = E\{\nu(T_i,Z_i,t)\}. \tag{12}$$

In view of (11) and (12), using inverse probability of censoring weighting techniques (Robins and Rotnitzky, 1992), we propose the following class of estimating equations for β_0 when the censoring time C_i may depend on Z_i under model (8),

$$U_b(\beta) = n^{-1}\sum_{i=1}^{n} \frac{\delta_i}{G_i(X_i;\hat\gamma,\hat\Lambda_0)}\Big\{h(\beta' Z_i)Z_i - \bar Z_i(\beta,\hat\gamma,\hat\Lambda_0)\Big\} = 0, \tag{13}$$

where

$$\bar Z_i(\beta,\gamma,\Lambda) = \int_0^{\tau} h(\beta' Z_i)Z_i g(\beta' Z_i)^{-2}(X_i - t)^+ L_n(t;\beta,\gamma,\Lambda)dt,$$

$$L_n(t;\beta,\gamma,\Lambda) = \frac{L_{1n}(t;\beta,\gamma,\Lambda)}{L_{2n}(t;\beta,\gamma,\Lambda)L_{3n}(t;\beta,\gamma,\Lambda)},$$

and $L_{kn}(t;\beta,\gamma,\Lambda) = n^{-1}\sum_{i=1}^n V_{ki}(t;\beta)G_i(X_i;\gamma,\Lambda)^{-1}, \quad k=1,\ 2,\ 3.$ Here

$$V_{1i}(t;\beta) = g(\beta' Z_i)^{-1}I(X_i > t)\delta_i, \qquad V_{2i}(t;\beta) = g(\beta' Z_i)^{-2}(X_i - t)^+\delta_i,$$

and $V_{3i}(t;\beta) = g(\beta' Z_i)^{-1}X_i\delta_i$.

Let $\hat\beta_b$ denote the solution to $U_b(\beta) = 0$. It can be shown in Appendix A.3 that $\hat\beta_b$ is consistent and unique in a neighborhood of β_0. To study the asymptotic distribution of $\hat\beta_b$, we first show that $n^{1/2}U_b(\beta_0)$ is asymptotically normal with zero mean and covariance matrix that can be consistently estimated by $\hat{\Sigma}_b$, where

$$\hat{\Sigma}_b = n^{-1}\sum_{i=1}^{n}\left[\hat{\xi}_i + \int_0^\tau \frac{R_n(t)}{S^{(0)}(t;\hat{\gamma})}d\hat{M}_i^c(t) + B_n D_n^{-1}\int_0^\tau \left\{Z_i - \bar{Z}_r(t;\hat{\gamma})\right\}d\hat{M}_i^c(t)\right]^{\otimes 2}, \qquad (14)$$

$$\hat{\xi}_i = \left\{h(\hat{\beta}_b' Z_i)Z_i - \bar{Z}_i(\hat{\beta}_b,\hat{\gamma},\hat{\Lambda}_0)\right\}\delta_i G_i(X_i;\hat{\gamma},\hat{\Lambda}_0)^{-1}$$
$$-\int_0^\tau Q_n(t)\left[\frac{\hat{\xi}_{1i}(t)}{\hat{L}_{2n}(t)\hat{L}_{3n}(t)} - \frac{\hat{L}_{1n}(t)\hat{\xi}_{2i}(t)}{\hat{L}_{2n}(t)^2\hat{L}_{3n}(t)} - \frac{\hat{L}_{1n}(t)\hat{\xi}_{3i}(t)}{\hat{L}_{2n}(t)\hat{L}_{3n}(t)^2}\right]dt,$$

$$R_n(t) = n^{-1}\sum_{i=1}^{n}\left\{h(\hat{\beta}_b' Z_i)Z_i - \bar{Z}_i(\hat{\beta}_b,\hat{\gamma},\hat{\Lambda}_0)\right\}\exp\{\hat{\gamma}' Z_i\}\delta_i G_i(X_i;\hat{\gamma},\hat{\Lambda}_0)^{-1}Y_i(t)$$
$$-\int_0^\tau Q_n(t)\left[\frac{R_{1n}(t,u)}{\hat{L}_{2n}(t)\hat{L}_{3n}(t)} - \frac{\hat{L}_{1n}(t)R_{2n}(t,u)}{\hat{L}_{2n}(t)^2\hat{L}_{3n}(t)} - \frac{\hat{L}_{1n}(t)R_{3n}(t,u)}{\hat{L}_{2n}(t)\hat{L}_{3n}(t)^2}\right]du,$$

$$B_n = n^{-1}\sum_{i=1}^{n}\left\{h(\hat{\beta}_b' Z_i)Z_i - \bar{Z}_i(\hat{\beta}_b,\hat{\gamma},\hat{\Lambda}_0)\right\}\hat{\Lambda}_0(X_i)\exp\{\hat{\gamma}' Z_i\}Z_i'\delta_i G_i(X_i;\hat{\gamma},\hat{\Lambda}_0)^{-1}$$
$$-n^{-1}\sum_{i=1}^{n}\int_0^\tau \left\{h(\hat{\beta}_b' Z_i)Z_i - \bar{Z}_i(\hat{\beta}_b,\hat{\gamma},\hat{\Lambda}_0)\right\}\exp\{\hat{\gamma}' Z_i\}\delta_i G_i(X_i;\hat{\gamma},\hat{\Lambda}_0)^{-1}$$
$$\times Y_i(t)\bar{Z}_r(t;\hat{\gamma})\}' d\hat{\Lambda}_0(t)$$
$$-\int_0^\tau Q_n(t)\left[\frac{P_{1n}(t)}{\hat{L}_{2n}(t)\hat{L}_{3n}(t)} - \frac{\hat{L}_{1n}(t)P_{2n}(t)}{\hat{L}_{2n}(t)^2\hat{L}_{3n}(t)} - \frac{\hat{L}_{1n}(t)P_{3n}(t)}{\hat{L}_{2n}(t)\hat{L}_{3n}(t)^2}\right]dt,$$

$$Q_n(t) = n^{-1}\sum_{i=1}^{n} h(\hat{\beta}_b' Z_i)Z_i g(\hat{\beta}_b' Z_i)^{-2}(X_i - t)^{+}\delta_i G_i(X_i;\hat{\gamma},\hat{\Lambda}_0)^{-1},$$

$$\hat{\xi}_{ki}(t) = V_{ki}(t;\hat{\beta}_b)G_i(X_i;\hat{\gamma},\hat{\Lambda}_0)^{-1} - \hat{L}_{kn}(t), \qquad k = 1,\ 2,\ 3,$$

$$R_{kn}(t,u) = n^{-1}\sum_{i=1}^{n} V_{ki}(t;\hat{\beta}_b)G_i(X_i;\hat{\gamma},\hat{\Lambda}_0)^{-1}\exp\{\hat{\gamma}' Z_i\}Y_i(u),$$

$$P_{kn}(t) = n^{-1}\sum_{i=1}^{n} V_{ki}(t;\hat{\beta}_b)G_i(X_i;\hat{\gamma},\hat{\Lambda}_0)^{-1}\hat{\Lambda}_0(X_i)\exp\{\hat{\gamma}' Z_i\}Z_i'$$
$$-\int_0^\tau R_{kn}(t,u)\bar{Z}_r(u;\hat{\gamma})' d\hat{\Lambda}_0(u),$$

$$\hat{M}_i^c(t) = N_i^c(t) - \int_0^t Y_i(u)\exp\{\hat{\gamma}' Z_i\}d\hat{\Lambda}_0(u),$$

$\hat{L}_{kn}(t) = L_{kn}(t; \hat{\beta}_b, \hat{\gamma}, \hat{\Lambda}_0)$, and $D_n = -\partial U_r(\hat{\gamma})/\partial \gamma'$. Then it follows that $n^{1/2}(\hat{\beta}_b - \beta_0)$ is asymptotically normal with zero mean and covariance matrix that can be consistently estimated by

$$\left\{ \frac{\partial U_b(\hat{\beta}_b)}{\partial \beta'} \right\}^{-1} \hat{\Sigma}_b \left\{ \frac{\partial U_b(\hat{\beta}_b)'}{\partial \beta} \right\}^{-1}.$$

To estimate the baseline mean residual life $m_0(t)$, define

$$M_i^*(t) = \frac{\delta_i I(X_i > t)}{G(X_i; \gamma_0, \Lambda_0)} \Big[(X_i - t) - m_0(t) g(\beta_0' Z_i) \Big], \quad i = 1, ..., n.$$

Under models (2) and (8), $M_i^*(t)$ are zero-mean stochastic processes. Thus, for given β, a reasonable estimator for $m_0(t)$ is the solution to

$$\sum_{i=1}^n \frac{\delta_i I(X_i > t)}{G_i(X_i; \hat{\gamma}, \hat{\Lambda}_0)} \Big[(X_i - t) - m_0(t) g(\beta' Z_i) \Big] = 0, \quad 0 \le t \le \tau.$$

Denote this estimator by $\hat{m}_{b0}(t; \beta)$, which can be expressed as

$$\hat{m}_{b0}(t; \beta) = \frac{\sum_{i=1}^n (X_i - t)^+ \delta_i G_i(X_i; \hat{\gamma}, \hat{\Lambda}_0)^{-1}}{\sum_{i=1}^n I(X_i > t) g(\beta' Z_i) \delta_i G_i(X_i; \hat{\gamma}, \hat{\Lambda}_0)^{-1}}. \tag{15}$$

Let $\hat{m}_{b0}(t) \equiv \hat{m}_{b0}(t; \hat{\beta}_b)$ be the corresponding estimator of the unknown baseline mean residual life $m_0(t)$ under models (2) and (8). Following the arguments of Appendix A.2 and A.3, we can check that $\hat{m}_{b0}(t)$ is consistent, and that $n^{1/2}\{\hat{m}_{b0}(t) - m_0(t)\}$ $(0 \le t \le \tau)$ converges weakly to a zero-mean Gaussian process whose covariance function at (s, t) can be estimated consistently by $\hat{\Gamma}_b(s, t) = n^{-1} \sum_{i=1}^n \hat{\psi}_i(s) \hat{\psi}_i(t)$, where

$$\hat{\psi}_i(t) = \hat{m}_{b0}(t) \bar{Z}_b(t; \hat{\beta}_b)' \left\{ \frac{\partial U_b(\hat{\beta}_b)}{\partial \beta'} \right\}^{-1} \Bigg[\hat{\xi}_i + B_n D_n^{-1} \int_0^\tau \{Z_i - \bar{Z}_r(u; \hat{\beta}_b)\} d\hat{M}_i^c(u)$$
$$+ \int_0^\tau \frac{R_n(u)}{S^{(0)}(u; \hat{\gamma})} d\hat{M}_i^c(u) \Bigg] + \Psi_n(t; \hat{\beta}_b)^{-1} \Bigg[\hat{M}_i^*(t) + \int_0^\tau \frac{r_n(t, u)}{S^{(0)}(u; \hat{\gamma})} d\hat{M}_i^c(u)$$
$$+ B_n^*(t) D_n^{-1} \int_0^\tau \{Z_i - \bar{Z}_r(u; \hat{\beta}_b)\} d\hat{M}_i^c(u) \Bigg],$$

$$\bar{Z}_b(t; \beta) = \frac{\sum_{i=1}^n I(X_i > t) h(\beta' Z_i) Z_i g(\beta' Z_i) \delta_i G(X_i; \hat{\gamma}, \hat{\Lambda}_0)^{-1}}{n \Psi_n(t; \beta)},$$

$$\Psi_n(t;\beta) = n^{-1}\sum_{i=1}^{n} I(X_i > t)g(\beta' Z_i)\delta_i G_i(X_i;\hat{\gamma},\hat{\Lambda}_0)^{-1},$$

$$\hat{M}_i^*(t) = I(X_i > t)\Big[(X_i - t) - \hat{m}_{b0}(t)g(\hat{\beta}_b' Z_i)\Big]\delta_i G_i(X_i;\hat{\gamma},\hat{\Lambda}_0)^{-1},$$

$$r_n(t,u) = n^{-1}\sum_{i=1}^{n} \hat{M}_i^*(t)\exp\{\hat{\gamma}' Z_i\}Y_i(u),$$

$$B_n^*(t) = n^{-1}\sum_{i=1}^{n} \hat{M}_i^*(t)\hat{\Lambda}_0(X_i)\exp\{\hat{\gamma}' Z_i\}Z_i' - \int_0^t r_n(t,u)\bar{Z}_r(u;\hat{\gamma})' d\hat{\Lambda}_0(u),$$

and $\hat{\xi}_i$, B_n, $R_n(u)$ and D_n are defined in (14).

Note that the limiting process of $n^{1/2}\{\hat{m}_{b0}(t) - m_0(t)\}$ is quite complicated, and its properties are difficult to obtain analytically. As discussed in Section 2, we can show that the distribution of the process $n^{1/2}\{\hat{m}_{b0}(t) - m_0(t)\}$ can be approximated by that of the zero-mean Gaussian process $\widehat{W}_b(t)$, where

$$\widehat{W}_b(t) = n^{-1/2}\sum_{i=1}^{n} \hat{\psi}_i(t)\Omega_i,$$

and $(\Omega_1, ..., \Omega_n)$ are independent standard normal variables which are independent of the data $\{X_i, \delta_i, Z_i; i = 1, ..., n\}$.

4. MODEL CHECKING TECHNIQUES

In this section, we develop testing procedures to check the adequacy of model (2) for both independent and dependent cases. Beginning with the independent case where censoring time C is independent of T and Z, let $G(t)$ be the survival function of C, and $\hat{G}(t)$ be the Kaplan-Meier estimate of $G(t)$ based on $\{X_i, 1 - \delta_i, i = 1, ..., n\}$, where

$$\hat{G}(t) = \prod_{s\le t}\left\{1 - \frac{\sum_{i=1}^n dN_i^c(s)}{\sum_{i=1}^n Y_i(s)}\right\}.$$

Define $H_1(t,z) = P\{X_i \le t, Z_i \le z, \delta_i = 1\}$, and $H(t,z) = P\{X_i \ge t, Z_i \le z\}$, where the notation "$Z_i \le z$" means that each component of Z_i is less than or equal to the corresponding component of z. After some algebraic manipulation, model (2) leads to

$$m_0(t) = \frac{1}{H(t,z)} \int_t^\tau \int_0^z \frac{(s-t)G(t)}{g(\beta_0' w)G(s)} H_1(ds, dw), \tag{16}$$

where $\int_0^z$ stands for $\int_0^{z_1} \dots \int_0^{z_p}$. Let us denote the right-hand side of (16) by $V(t,z)$. Note that the left-hand side is independent of the variable z. As a measure of fit for model (2), we estimate $V(t,z)$ by $V_n(t,z)$ and obtain the process

$$\theta_n(t,z) = n^{1/2}\{V_n(t,z) - V_n(t,z_u)\}, \tag{17}$$

where z_u is the vector of upper bounds for Z,

$$V_n(t,z) = \frac{1}{H_n(t,z)} \left\{ \int_t^\tau \int_0^z \frac{(s-t)\hat{G}(t)}{g(\hat{\beta}_a' w)\hat{G}(s)} H_{1n}(ds, dw) \right\},$$

and H_n and H_{1n} are the empirical counterparts of H and H_1, respectively. That is, $H_n(t,z) = n^{-1}\sum_{i=1}^n I(X_i \ge t, Z_i \le z)$ and $H_{1n}(t,z) = n^{-1}\sum_{i=1}^n I(X_i \le t, Z_i \le z, \delta_i = 1)$. Under model (2), the process $\theta_n(t,z)$ equals $\phi_n(t,z) - \phi_n(t,z_u)$, where $\phi_n(t,z) = n^{1/2}\{V_n(t,z) - V(t,z)\}$ is the standardized mean residual life process. Hence, based on (17), the Kolmogorov-Smirnov (KS) type test statistic $\mathcal{F}_n^{(1)}$ may be used to check the adequacy of model (2), where

$$\mathcal{F}_n^{(1)} = \sup_{t,z} |\theta_n(t,z)|.$$

Under model (2), we show in Appendix A.4 that $\theta_n(t,z)$ converges to a zero-mean Gaussian process $W(t,z)$ whose covariance function at (t,z) and (t^*,z^*) can be estimated consistently by $\hat{\sigma}(t,z;t^*,z^*) = n^{-1}\sum_{i=1}^n \hat{\eta}_i(t,z)\hat{\eta}_i(t^*,z^*)$, where $\hat{\eta}_i(t,z) = \hat{\rho}_i(t,z) - \hat{\rho}_i(t,z_u)$,

$$\hat{\rho}_i(t,z) = \frac{\hat{G}(t)}{H_n(t,z)} \int_t^\tau \left[\int_u^\tau \int_0^z \frac{s-t}{\hat{G}(s)g(\hat{\beta}_a' w)} H_{1n}(ds,dw) \right] \frac{d\widetilde{M}_i^c(u)}{\pi_n(u)}$$
$$+ \frac{\delta_i (X_i - t)\hat{G}(t)}{H_n(t,z)\hat{G}(X_i)g(\hat{\beta}_a' Z_i)} I(X_i \ge t, Z_i \le z) - \frac{V_n(t,z)}{H_n(t,z)} I(X_i \ge t, Z_i \le z)$$

$$+\frac{\hat{G}(t)}{H_n(t,z)}\int_t^{\tau}\int_0^{z}\frac{(s-t)h(\hat{\beta}_a' w)w'}{\hat{G}(s)g(\hat{\beta}_a' w)}H_{1n}(ds,dw)\hat{A}^{-1}\int_0^{\tau}\left\{h(\hat{\beta}_a' Z_i)Z_i-\hat{\mu}(u)\right\}$$
$$\times\left[\hat{m}_{a0}(u)dN_i(u)-Y_i(u)\left\{g(\hat{\beta}_a' Z_i)^{-1}du+d\hat{m}_{a0}(u)\right\}\right], \qquad (18)$$

$$d\hat{m}_{a0}(u)=\frac{\sum_{j=1}^{n}[\hat{m}_{a0}(u)dN_j(u)-Y_j(u)g(\hat{\beta}' Z_j)^{-1}du]}{\sum_{j=1}^{n}Y_j(u)},$$

$$d\widetilde{M}_i^c(u)=dN_i^c(u)-Y_i(u)d\Lambda_n^c(u),$$

and $d\Lambda_n^c(u) = n^{-1}\sum_{i=1}^{n} dN_i^c(u)/\pi_n(u)$. Consequently, $\mathcal{F}_n$ converges in distribution to $\mathcal{F}$, where

$$\mathcal{F}=\sup_{t,z}|W(t,z)|.$$

Obviously, the complicated structure of the covariance function (18) does not allow for an analytic treatment of the involved distributions. As discussed in Sections 2 and 3, we can show that the distribution of the process $W(t,z)$ can be approximated by that of the zero-mean Gaussian process $\widetilde{W}(t,z)$, where

$$\widetilde{W}(t,z)=n^{-1/2}\sum_{i=1}^{n}\hat{\eta}_i(t,z)\Omega_i,$$

and $(\Omega_1,...,\Omega_n)$ are independent standard normal variables which are independent of the data $\{X_i,\delta_i,Z_i; i=1,...,n\}$. Thus, the distributions of $\mathcal{F}$ can be approximated by $\tilde{\mathcal{F}}$, where

$$\tilde{\mathcal{F}}=\sup_{t,z}|\widetilde{W}(t,z)|.$$

To approximate the distribution of $\mathcal{F}$, we obtain a large number, say M, of realizations from $\tilde{\mathcal{F}}$ by repeatedly generating the normal random sample $(\Omega_1,...,\Omega_n)$ while fixing the data $\{X_i,\delta_i,Z_i; i=1,...,n\}$ at their observed values. Then using this simulation method, we may determine an approximate critical value of the test. Specifically, the p-value of the test can be obtained as follows,

$$p=\frac{1}{M}\sum_{k=1}^{M}I(\tilde{\mathcal{F}}_k>\mathcal{F}_n),$$

where $\tilde{\mathcal{F}}_k$ $(k=1,...,M)$ are M realizations from $\tilde{\mathcal{F}}$.

For the dependent case where C depends on Z, an analogous procedure can be developed. Let $G(t|z)$ be the censoring survival distribution of C given $Z = z$, and

$$\hat{G}(t|z) = \exp\big\{ -\hat{\Lambda}_0(t)\exp(\hat{\gamma}'z)\big\}.$$

After some algebraic manipulation, model (2) leads to

$$m_0(t) = \frac{1}{H(t,z)} \int_t^{\tau}\int_0^{z} \frac{(s-t)G(t|w)}{g(\beta_0'w)G(s|w)} H_1(ds,dw). \tag{19}$$

Let us denote the right-hand side of (19) by $V^*(t,z)$. Note again that the left-hand side is independent of the variable z, and $V^*(t,z)$ can be estimated by $V_n^*(t,z)$, where

$$V_n^*(t,z) = \frac{1}{H_n(t,z)} \left\{ \int_t^{\tau}\int_0^{z} \frac{(s-t)\hat{G}(t|w)}{g(\hat{\beta}_b'w)\hat{G}(s|w)} H_{1n}(ds,dw) \right\}.$$

Similarly, for check the adequacy of model (2) under the dependent case, we use the Kolmogorov-Smirnov type test statistic $\mathcal{F}_n^{(2)}$, where

$$\mathcal{F}_n^{(2)} = \sup_{t,z} |\theta_n^*(t,z)|,$$

and $\theta_n^*(t,z) = n^{1/2}\{V_n^*(t,z) - V_n^*(t,z_u)\}$.

Under model (2), we can also show that $\theta_n^*(t,z)$ converges to a zero-mean Gaussian process $W^*(t,z)$ whose covariance function at (t,z) and $(t^\dagger, z^\dagger)$ can be estimated consistently by $\hat{\sigma}^*(t,z;t^\dagger,z^\dagger) = n^{-1}\sum_{i=1}^n \hat{\eta}_i^*(t,z)\hat{\eta}_i^*(t^\dagger,z^\dagger)$, where $\hat{\eta}_i^*(t,z) = \hat{\rho}_i^*(t,z) - \hat{\rho}_i^*(t,z_u)$,

$$\begin{aligned}
\hat{\rho}_i^*(t,z) = {} & \frac{1}{H_n(t,z)}\int_t^{\tau}\left[\int_u^{\tau}\int_0^{z}\frac{(s-t)\exp\{\hat{\gamma}'w\}\hat{G}(t|w)}{g(\hat{\beta}_b'w)\hat{G}(s|w)}H_{1n}(ds,dw)\right]\frac{d\hat{M}_i^c(u)}{S^{(0)}(u;\hat{\gamma})} \\
& + \frac{1}{H_n(t,z)}\int_t^{\tau}\int_0^{z}\frac{(s-t)\exp\{\hat{\gamma}'w\}\hat{G}(t|w)}{g(\hat{\beta}_b'w)\hat{G}(s|w)}\left[\int_t^{s}(w-\bar{Z}_r(v;\hat{\beta}_b)'d\hat{\Lambda}_0(v)\right] \\
& \times H_{1n}(ds,dw)D_n^{-1}\int_0^{\tau}\big\{Z_i - \bar{Z}_r(u;\hat{\beta}_b)\big\}d\hat{M}_i^c(u) \\
& + \frac{\delta_i(X_i-t)\hat{G}(t|Z_i)}{H_n(t,z)\hat{G}(X_i|Z_i)g(\hat{\beta}_b'Z_i)}I(X_i \ge t, Z_i \le z) - \frac{V_n(t,z)}{H_n(t,z)}I(X_i \ge t, Z_i \le z)
\end{aligned}$$

$$+\frac{1}{H_n(t,z)}\int_t^\tau\int_0^z \frac{(s-t)h(\hat{\beta}_b'w)\hat{G}(t|w)w'}{\hat{G}(s|w)g(\hat{\beta}_b'w)}H_{1n}(ds,dw)\left\{\frac{\partial U_b(\hat{\beta}_b)}{\partial\beta'}\right\}^{-1}$$
$$\times\left[\hat{\xi}_i+\int_0^\tau \frac{R_n(u)}{S^{(0)}(u;\hat{\gamma})}d\hat{M}_i^c(u)+B_nD_n^{-1}\int_0^\tau\{Z_i-\bar{Z}_r(u;\hat{\beta}_b)\}d\hat{M}_i^c(u)\right]. \qquad (20)$$

Consequently, $\mathcal{F}_n^{(2)}$ converges in distribution to $\mathcal{F}^*=\sup_{t,z}|W^*(t,z)|$. As in the independent case, we can show that the distribution of the process $W^*(t,z)$ can be approximated by that of the zero-mean Gaussian process $\widetilde{W}^*(t,z)=n^{-1/2}\sum_{i=1}^n\hat{\eta}_i^*(t,z)\Omega_i$ based on (20). Thus, the distributions of $\mathcal{F}^*$ can be approximated by $\tilde{\mathcal{F}}^*=\sup_{t,z}|\widetilde{W}^*(t,z)|$, and the p-value of the test can be obtained in the same way as before.

5. SIMULATION STUDIES

We conducted simulation studies to assess the performance of the estimation procedure proposed in Sections 2 and 3 with the focus on estimating β_0. In the study, the survival time T was generated from model (2) with $\beta_0=0$ or 0.5, and the baseline mean residual life function was taken to be $m_0(t)=-0.5t+1$, which corresponds to a rescaled beta distribution (Oakes and Dasu, 1990). The covariate Z was assumed to be a Bernoulli random variable with success probability 0.5. We considered three choices for the link function $g(x)$: $g_1(x)=1+x$, $g_2(x)=e^x$ and $g_3(x)=\log(1+e^x)$. The censoring time C was generated from the exponential distribution with hazard rate $\lambda_0e^{\gamma_0Z}$ for $\gamma_0=0$ or 1, and λ_0 was chosen to result in two censoring percentages of approximately 10% and 30%. Note that $\gamma_0=0$ corresponds to independent censoring times, while $\gamma_0=1$ gives dependent censoring times. The results presented below are based on $n=100$ or 200 with 2000 replications.

Table 1 shows the results for independent censoring ($\gamma_0=0$). It can been seen that the bias for estimating β_0 is very small and the standard error of the estimator is very accurate for all settings. The 95% empirical coverage probability based on normal approximation are reasonable, and the results become better when the sample size increases from 100 to 200. Table 2 shows similar results for dependent censoring ($\gamma_0 = 1$).

To investigate the asymptotical normality of the proposed estimates of β_0 under both independent and dependent censoring, we provide some QQ-plots in Figure 1, which suggest reasonable normal approximations to the finite-sample distributions of the proposed estimators. We also considered other models and set-ups and obtained similar results.

6. AN APPLICATION

We applied the proposed estimation procedures to a data set from a clinic trial on lung cancer that has previous been analyzed by others (Lad et al., 1988, Piantadosi, 2005, and Chen et al. 2005). The purpose of the trial is to assess the impact of systematic combination chemotherapy on patients' survival. Specifically, survival time of interest includes both time to death and disease-free survival time. Between November 1979 and May 1985, 172 patients were randomized to receive either postoperative radiotherapy (RT) alone or postoperative RT plus chemotherapy with Cytoxan, Adriamycin, and Platinol (RT + CAP) for 6 months and followed until death. The mean follow-up time is 1.5 years. Only 164 patients were eligible for analysis, among which 86 patients were in RT and 78 in RT + CAP group.

In our analysis, we consider examining the effect of treatment and cell type (squamous vs. nonsquamous/mixed) on patients' disease-free survival. For treatment, we let $Z_1 = 1$ if the patient is in RT + CAP group and 0 otherwise. For cell type, we let $Z_2 = 1$ if the patient had the squamous cell type and 0 otherwise. We first fit model (8) containing both covariates to the data to determine whether dependent or independent case should be considered. The logrank test shows that the overall effect of treatment and cell type on the censoring time is insignificant with a p-value of 0.876. The Kaplan-Meier estimates of survival functions of the censoring time for four subgroups were plotted in Figure 2 (a). Thus, for the illustration purpose, we then fit model (2) to the data only under the independent censoring situation.

Table 3 shows that the estimation and test of hypothesis results for the effect of each of the covariates by using three different functions for g. The results show that both treatment and cell type have significant effect on the patients' disease-free survival after adjusting the effect of the other. More specifically, patients in RT + CAP group have significantly longer mean residual disease-free life than those in the RT group, and patients having squamous cell type have significantly longer mean residual disease-free life than those having nonsquamous/mixed cell type. Figure 2 (b) and (c) show the difference in survival functions between the treatment groups and two cell type groups, respectively. This is consistent with the results from Chen et al. (2005) under the proportional mean residual life model and from Piantadosi (2005) under the proportional hazards model. Note that the three functions for g yield similar results, and the result from $g(x) = e^x$ is the least conservative based on the p-values.

We also checked the adequacy of model (2) with both covariate under the three functions of $g(x)$. Based on 500 realizations of $\tilde{\mathcal{F}}$, the KS-type test statistics with p-values in parentheses, are 4288.81 (0.966), 4554.43 (0.946) and 6341.43 (0.958) for $g(x)$ to be $1 + x$, e^x and $\log(1 + e^x)$, respectively. These results indicate that model (2) fits the data adequately.

7. CONCLUDING REMARKS

In this article we have studied a class of mean residual life regression models under both independent and dependent censoring. The proposed models are generalization of the proportional mean residual life model with more choices of the link function $g(x)$. Estimation procedures were proposed for the model parameters, and asymptotic properties of the estimators were derived. The methodology was applied to a cancer data set from a clinic trial, and the simulation results show that the proposed methods work well for the situations considered.

As it is well-known, model checking is always an important issue in regression analysis, because most regression models have limitations. We proposed a goodness of fit test for model (2) based on the KS type test statistics. In addition, the Cramér-von Mises type test statistics can also be used to check the adequacy of model (2):

$$\mathcal{F}_n^{(3)} = \int\int \theta_n(t,z)^2 H_n^0(dt,dz),$$

which converges in distribution to

$$\mathcal{F}^{(3)} = \int\int W(t,z)^2 H^0(dt,dz),$$

where H^0 and H_n^0 are the distribution function and empirical distribution function of (X_i, Z_i), respectively. Similar to the KS-type test statistics, $\tilde{\mathcal{F}}^{(3)} = \int\int \widetilde{W}(t,z)^2 H_n^0(dt,dz)$ can be used to approximate the distribution of $\mathcal{F}^{(3)}$.

For dependent censoring, the proportional hazards model was used as the working model for the censoring time. Of course, we can also choose some other semiparametric regression models as the working model for censoring. For example, we may use the proportional mean residual life model or the additive mean residual life model, then we can obtain the estimators of the censoring model parameters using the approach of Chen and Cheng (2005) or Chen and Cheng (2006). Thus, the estimator of the censoring survival distribution $G(t|z)$ can be obtained using the following inversion formula

$$G(t|z) = \frac{m_G(0|z)}{m_G(t|z)} \exp\Big\{ - \int_0^t m_G(u|z)^{-1} du \Big\},$$

where $m_G(t|z) = E(C - t|z, C > t)$ is the MRLF of C at t given z. Thus, the unknown parameter in model (2) can be estimated by using the procedure in Section 3.

Since estimating functions (7) and (13) were given in a somewhat ad hoc fashion using the generalized estimating equation methods, it would be worthwhile to further investigate the efficiencies of the proposed estimators. In principle, it might be possible to estimate β_0 and $m_0(\cdot)$ more efficiently by the nonparametric maximum likelihood approach, and the resulting inference procedure would be much more complicated. Another issue is that the estimates of $m_0(t)$ may be not monotonic, and there is no guarantee that the finite-sample estimator $\hat{m}_{a0}(t)+t$ or $\hat{m}_{b0}(t)+t$ would maintain the necessary monotonicity at some time point. The incorporation of the pooled-adjacent-violators algorithm may help solving the problem as mentioned in Chen and Cheng (2005).

ACKNOWLEDGEMENTS

This research was partly supported by the National Natural Science Foundation of China Grants (No. 10571169 and 10731010) and the National Basic Research Program of China (973 Program) (No. 2007CB814902).

APPENDIX: PROOFS OF ASYMPTOTIC PROPERTIES

Using the uniform strong law of large numbers (Pollard, 1990, p.41), we have $\bar{z}_a(t) = \lim_{n\to} \bar{Z}_a(t;\beta_0)$, and $s^{(k)}(t;\gamma) = \lim_{n\to\infty} S^{(k)}(t;\gamma)$ $(k=0,1)$ uniformly in $t\in[0,\tau]$. Let $\bar{z}_r(t) = s^{(1)}(t;\gamma_0)/s^{(0)}(t;\gamma_0)$. In addition, assume that A defined below in (A.4) is nonsingular matrix.

A.1. ASYMPTOTIC NORMALITY OF $U_a(\beta_0)$ AND $\hat{\beta}_a$

Note that

$$\sum_{i=1}^{n}\left[m_0(t)dN_i(t) - Y_i(t)\left\{g(\beta_0'Z_i)^{-1}dt + dm_0(t)\right\}\right] = m_0(t)\sum_{i=1}^{n} dM_i(t),$$

and

$$\sum_{i=1}^{n}\left[\hat{m}_{a0}(t;\beta_0)dN_i(t)-Y_i(t)\big\{g(\beta_0'Z_i)^{-1}dt+d\hat{m}_{a0}(t;\beta_0)\big\}\right]=0.$$

Then it follows that

$$\{\hat{m}_{a0}(t;\beta_0)-m_0(t)\}\sum_{i=1}^{n}dN_i(t)-n\pi_n d\{\hat{m}_{a0}(t;\beta_0)-m_0(t)\}=-m_0(t)\sum_{i=1}^{n}dM_i(t),$$

which is a first-order linear ordinary differential equation in $\hat{m}_{a0}(t;\beta_0)-m_0(t)$. It thus has the closed-form solution given by

$$\hat{m}_{a0}(t;\beta_0)-m_0(t)=-\Phi_n(t)^{-1}\sum_{i=1}^{n}\int_t^{\tau}\frac{\Phi_n(u)m_0(u)}{n\pi_n(u)}dM_i(u). \qquad (A.1)$$

Write

$$U_a(\beta_0)=n^{-1}\sum_{i=1}^{n}\int_0^{\tau}\left\{h(\beta_0'Z_i)Z_i-\bar{Z}_a(t;\beta_0)\right\}m_0(t)dM_i(t)$$

$$+n^{-1}\sum_{i=1}^{n}\int_0^{\tau}\left\{h(\beta_0'Z_i)Z_i-\bar{Z}_a(t;\beta_0)\right\}\left[\hat{m}_{a0}(t;\beta 0)-m_0(t)\right]dN_i(t).$$

Using the uniform strong law of large numbers and (A.1), the second term in the right-hand side of the above equation is equivalent to

$$-n^{-1}\sum_{i=1}^{n}\int_0^{\tau}\mu_*(t)m_0(t)dM_i(t)+o_p(n^{-1/2}),$$

where

$$\mu_*(t)=\frac{S(t)}{\pi(t)}\int_0^t\frac{1}{S(u)}E\Big[\{h(\beta'Z_i)Z_i-\bar{z}_a(u)\}dN_i(u)\Big],$$

$\pi(t)=EY_1(t)$, and $S(t)$ is the marginal survival function of T. Therefore,

$$n^{1/2}U_a(\beta_0)=n^{-1/2}\sum_{i=1}^{n}\int_0^{\tau}\left\{h(\beta_0'Z_i)Z_i-\mu(t)\right\}m_0(t)dM_i(t)+o_p(1),$$

where $\mu(t)=\bar{z}_a(t)+\mu_*(t)$. As a result, $n^{1/2}U_a(\beta_0)$ converges in distribution to zero-mean normal distribution with covariance matrix Σ_a, where

$$\Sigma_a=E\left[\int_0^{\tau}\Big\{h(\beta_0'Z_i)Z_i-\mu(t)\Big\}^{\otimes 2}m_0(t)^2dN_i(t)\right], \qquad (A.2)$$

which can be consistently estimated by $\hat{\Sigma}_a$ defined in Section 2.

Since the censoring time C is independent of T and Z, and

$$\int_t^\tau S(u|Z)g(\beta_0'Z)^{-1}du = m_0(t)S(t|Z),$$

under model (2), it follows from the uniform strong law of large numbers that

$$\begin{aligned}\frac{\partial \hat{m}_{a0}(t;\beta_0)}{\partial\beta} &= -\Phi_n(t)^{-1}\int_t^\tau \frac{\Phi_n(u)}{\pi_n(u)}\Big[n^{-1}\sum_{i=1}^n Y_i(u)h(\beta_0'Z_i)g(\beta_0'Z_i)^{-1}Z_i du\Big] \\ &= -\frac{1}{S(t)}E\left[h(\beta_0'Z_i)Z_i\int_t^\tau S(u|Z_i)g(\beta_0'Z_i)^{-1}du\right] + o_p(1) \\ &= -m_0(t)\bar{z}_a(t) + o_p(1). \qquad (A.3)\end{aligned}$$

Let $\hat{A} = n^{-1}\partial U(\beta_0)/\partial\beta'$, and $h^{(1)}(x) = dh(x)/dx$. Then it follows from (A.3) that

$$\begin{aligned}\hat{A} &= n^{-1}\sum_{i=1}^n\int_0^\tau\left\{h^{(1)}(\beta_0'Z_i)Z_i^{\otimes 2} - \frac{\sum_{i=1}^n Y_i(t)h^{(1)}(\beta_0'Z_i)Z_i^{\otimes 2}}{\sum_{i=1}^n Y_i(t)}\right\} \\ &\quad\times\left[\hat{m}_{a0}(t;\beta_0)dN_i(t) - Y_i(t)g(\beta_0'Z_i)^{-1}dt\right] \\ &\quad + n^{-1}\sum_{i=1}^n\int_0^\tau\left\{h(\beta_0'Z_i)Z_i - \bar{Z}_a(t;\beta_0)\right\}\left[\frac{\partial\hat{m}_{a0}(t;\beta_0)}{\partial\beta'}dN_i(t) + Y_i(t)h(\beta_0'Z_i)Z_i'g(\beta_0'Z_i)^{-1}dt\right] \\ &= n^{-1}\sum_{i=1}^n\int_0^\tau\left\{h^{(1)}(\beta_0'Z_i)Z_i^{\otimes 2} - \frac{\sum_{i=1}^n Y_i(t)h^{(1)}(\beta_0'Z_i)Z_i^{\otimes 2}}{\sum_{i=1}^n Y_i(t)}\right\}\Big[m_0(t)dM_i(t) + Y_i(t)dm_0(t)\Big] \\ &\quad - n^{-1}\sum_{i=1}^n\int_0^\tau\left\{h(\beta_0'Z_i)Z_i - \bar{Z}_a(t;\beta_0)\right\}\Big[z_a(t)'\Big\{m_0(t)dM_i(t) + Y_i(t)g(\beta_0'Z_i)^{-1}dt \\ &\quad + Y_i(t)dm_0(t)\Big\} - Y_i(t)h(\beta_0'Z_i)Z_i'g(\beta_0'Z_i)^{-1}dt\Big] + o_p(1) \\ &= A + o_p(1),\end{aligned}$$

where

$$A = E\left[\int_0^\tau\{h(\beta_0'Z_i)Z_i - \bar{z}_a(t)\}^{\otimes 2}Y_i(t)g(\beta_0'Z_i)^{-1}dt\right]. \qquad (A.4)$$

Thus, the asymptotic distribution of $\hat{\beta}_a$ follows from a Taylor series expansion of $U_a(\hat{\beta}_a)$ at β_0. For future reference, we display the asymptotic approximation

$$n^{1/2}(\hat{\beta}_a - \beta_0) = -A^{-1}n^{-1/2}\sum_{i=1}^n\int_0^\tau\{h(\beta_0'Z_i)Z_i - \mu(t)\}\,m_0(t)dM_i(t) + o_p(1). \qquad (A.5).$$

A.2. WEAK CONVERGENCE OF $\hat{m}_{a0}(t)$

To show the weak convergence of $n^{1/2}\{\hat{m}_{a0}(t) - m_0(t)\}$, we first note that

$$n^{1/2}\{\hat{m}_{a0}(t) - m_0(t)\} = n^{1/2}\{\hat{m}_{a0}(t;\beta_0) - m_0(t)\} + n^{1/2}\{\hat{m}_{a0}(t;\hat{\beta}_a) - \hat{m}_0(t;\beta_0)\}.$$

It follows from (A.1) and the uniform strong law of large numbers that

$$n^{1/2}\{\hat{m}_{a0}(t;\beta_0) - m_0(t)\} = -S(t)^{-1}n^{-1/2}\sum_{i=1}^{n}\int_t^\tau \frac{S(u)m_0(u)}{\pi(u)}dM_i(u) + o_p(1).$$

Using the Taylor expansion of $\hat{m}_{a0}(t;\hat{\beta}_a)$ together with (A.3), we have

$$n^{1/2}\{\hat{m}_{a0}(t;\hat{\beta}_a) - \hat{m}_{a0}(t;\beta_0)\} = -m_0(t)\bar{z}_a(t)'n^{1/2}\{\hat{\beta}_a - \beta_0\} + o_p(1).$$

Thus, it follows from (A.5) that

$$n^{1/2}\{\hat{m}_{a0}(t) - m_0(t)\} = n^{-/2}\sum_{i=1}^{n}\varphi_i(t) + o_p(1),$$

where

$$\varphi_i(t) = -S(t)^{-1}\int_t^\tau \frac{S(u)m_0(u)}{\pi(u)}dM_i(u) + m_0(t)\bar{z}_a(t)'A^{-1}\int_0^\tau \{h(\beta_0'Z_i)Z_i - \mu(u)\}\, m_0(u)dM_i(u).$$

Because φ_i $(i = 1, ..., n)$ are independent zero-mean random variables for each t, the multivariate central limit theorem implies that $n^{1/2}\{\hat{m}_{a0}(t) - m_0(t)\}$ $(0 \le t \le \tau)$ converges in finite-dimensional distributions to zero-mean Gaussian process. Using the modern empirical theory as Lin et al. (2000) and Lin, Wei and Ying (2001), we can show that $n^{1/2}\{\hat{m}_{a0}(t) - m_0(t)\}$ is tight and converges weakly to zero-mean Gaussian process with covariance function $\Gamma_a(s,t) = E\{\varphi_i(s)\varphi_i(t)\}$ at (s,t), which can be estimated by $\hat{\Gamma}_a(s,t)$ given in Section 2.

A.3. ASYMPTOTIC NORMALITY OF $U_b(\beta_0)$ AND $\hat{\beta}_b$

It can be checked that

$$U_b(\beta_0) = n^{-1}\sum_{i=1}^{n}\left\{h(\beta_0'Z_i)Z_i - \tilde{Z}_i\right\}\delta_i G(X_i;\gamma_0,\Lambda_0)^{-1}$$
$$+n^{-1}\sum_{i=1}^{n}\left\{h(\beta_0'Z_i)Z_i - \tilde{Z}_i\right\}\delta_i\left[\hat{G}_i(X_i;\hat{\gamma},\hat{\Lambda}_0)^{-1} - G(X_i;\gamma_0,\Lambda_0)^{-1}\right]$$
$$-\int_0^\tau Q(t)\left\{L_n(t;\beta_0,\hat{\gamma},\hat{\Lambda}_0) - L(t)\right\}dt + o_p(n^{-1/2}), \qquad (A.6)$$

where $Q(t) = \lim_{n\to\infty} Q_n(t)$, $L(t) = L_1(t)/(L_2(t)L_3(t))$, $L_k(t) = \lim_{n\to\infty} L_{kn}(t;\beta_0,\gamma_0,\Lambda_0)$ $(k = 1,2,3)$, and

$$\tilde{Z}_i = \int_0^\tau h(\beta_0'Z_i)Z_i g(\beta_0'Z_i)^{-2}(X_i - t)^+ L(t)dt.$$

It is well known that (Fleming and Harrington, 1991, p.299)

$$\hat{\Lambda}_0(t) - \Lambda_0(t) = n^{-1}\sum_{i=1}^{n}\int_0^t \frac{dM_i^c(u)}{s^{(0)}(u;\gamma_0)} - \int_0^t \bar{z}_r(u)'d\Lambda_0(u)(\hat{\gamma} - \gamma_0) + o_p(n^{-1/2}),$$

$$\hat{\gamma} - \gamma_0 = D^{-1}n^{-1}\sum_{i=1}^{n}\int_0^\tau \left\{Z_i - \bar{z}_r(u)\right\}dM_i^c(u) + o_p(n^{-1/2}),$$

$$M_i^c(t) = N_i^c(t) - \int_0^t Y_i(u)\exp\{\gamma_0'Z_i\}d\Lambda_0(u),$$

and $D = \lim_{n\to\infty} D_n$. Thus,

$$L_{kn}(t;\beta_0,\hat{\gamma},\hat{\Lambda}_0) - L_{kn}(t;\beta_0,\gamma_0,\Lambda_0) = n^{-1}\sum_{i=1}^{n}\int_0^\tau \frac{R_k(t,u)}{s^{(0)}(u)}dM_i^c(u) + P_k(t)(\hat{\gamma} - \gamma_0) + o_p(n^{-1/2}),$$

and

$$L_{kn}(t;\beta_0,\gamma_0,\Lambda_0) - L_k(t) = n^{-1}\sum_{i=1}^{n}\xi_{ki}(t) + o_p(n^{-1/2}),$$

where $\xi_{ki}(t) = V_{ki}(t;\beta_0)G_i(t;\gamma_0,\Lambda_0)^{-1} - L_k(t)$, and $R_k(t,u)$ and $P_k(t)$ are the limits of $R_{kn}(t,u)$ and $P_{kn}(t)$, respectively. Therefore, using the functional Delta-method, it follows from (A.6) that

$$n^{1/2}U_b(\beta_0) = n^{-1/2}\sum_{i=1}^{n}\left[\xi_i + \int_0^\tau \frac{R(t)}{S^{(0)}(t;\hat{\gamma})}dM_i^c(t) + BD^{-1}\int_0^\tau \left\{Z_i - \bar{z}_r(t)\right\}dM_i^c(t)\right] + o_p(1),$$

where

$$\xi_i = \frac{\delta_i\{h(\beta_0' Z_i)Z_i - \tilde{Z}_i\}}{G_i(X_i; \gamma_0, \Lambda_0)} - \int_0^\tau Q(t)\left[\frac{\xi_{1i}(t)}{L_2(t)\hat{L}_3(t)} - \frac{L_1(t)\xi_{2i}(t)}{L_2(t)^2 L_3(t)} - \frac{L_1(t)\xi_{3i}(t)}{L_2(t)L_3(t)^2}\right] dt,$$

and $R(t)$ and B are the limits of $R_n(t)$ and B_n given in (14), respectively. Utilizing the multivariate central limit theorem, $n^{1/2}U_b(\beta_0)$ is asymptotically normal with mean zero and covariance matrix Σ_b, where

$$\Sigma_b = E\left[\xi_i + \int_0^\tau \frac{R(t)}{S^{(0)}(t;\hat{\gamma})} dM_i^c(t) + BD^{-1}\int_0^\tau \{Z_i - \bar{z}_r(t)\} dM_i^c(t)\right]^{\otimes 2}.$$

An empirical covariance estimator $\hat{\Sigma}_b$ defined by (14), in which all unknown quantities are replaced with their observed counterparts, converges in probability to Σ_b.

It can be checked that $U_b(\beta)$ converges almost surely uniformly in a closed set of β to $u_b(\beta)$, and $u_b(\beta_0) = 0$, where

$$u_b(\beta) = E\{h(\beta' Z)Z\} - \int_0^\tau \frac{E\{h(\beta' Z)Zg(\beta' Z)^{-2}(T-t)^+\}}{E\{g(\beta' Z)^{-2}(T-t)^+\}} \frac{E\{g(\beta' Z)^{-1}I(T>t)\}}{E\{g(\beta' Z)^{-1}T\}} dt.$$

For any function $w(Z)$, define

$$E_{t,\beta_0}\{w(Z)\} = \frac{E\{w(Z)g(\beta_0' Z)^{-2}(T-t)^+\}}{E\{g(\beta_0' Z)^{-2}(T-t)^+\}},$$

and

$$E_{\beta_0}\{w(Z)\} = \frac{E\{w(Z)g(\beta_0' Z)^{-1}T\}}{E\{g(\beta_0' Z)^{-1}T\}}.$$

Then

$$\frac{\partial u_b(\beta_0)}{\partial \beta'} = 2\int_0^\tau \mathrm{Var}_{t,\beta_0}\{h(\beta_0' Z)Z\} E_{\beta_0}\{S(t|Z)m(0|Z)^{-1}\}$$

$$-\frac{1}{m_0(0)}\int_0^\tau \mathrm{Cov}_{\beta_0}\{h(\beta_0' Z)Z, S(t|Z)\}\ \mathrm{Cov}_{t,\beta_0}\{h(\beta_0' Z)Z, g(\beta_0' Z)^{-1}\} dt.$$

We observe that $S(t|Z)$ is decreasing function of $g(\beta_0' Z)^{-1}$, which implies that $\{h(\beta_0' Z), S(t|Z)\}$ and $\mathrm{cov}_{t,\beta_0}\{h(\beta_0' Z)Z, g(\beta_0' Z)^{-1}\}$ must take opposite signs (Maguluri and Zhang, 1994). This gives that $\partial u_b(\beta_0)/\partial \beta'$ is positive definite. Thus, it follows that $\hat{\beta}_b$ is consistent and unique in a neighborhood of β_0. A Taylor series expansion of $U_b(\hat{\beta}_b)$ yields that $n^{1/2}(\hat{\beta}_b - \beta_0)$ is asymptotically normal with mean zero and covariance matrix given by

$$\left\{\frac{\partial u_b(\beta_0)}{\partial \beta'}\right\}^{-1} \Sigma_b \left\{\frac{\partial u_b(\beta_0)'}{\partial \beta}\right\}^{-1}.$$

A.4. WEAK CONVERGENCE OF $\theta_n(t, z)$

It can be checked that

$$\phi_n(t,z) = \frac{n^{1/2}\{B_n(t,z) - B(t,z)\}}{H(t,z)} - \frac{B(t,z)}{H(t,z)^2} n^{1/2}\{H_n(t,z) - H(t,z)\} + o_p(1), \qquad (A.7)$$

where

$$B_n(t,z) = \int_t^\tau \int_0^z \frac{(s-t)\hat{G}(t)}{g(\hat{\beta}_a' w)\hat{G}(s)} H_{1n}(ds, dw),$$

and

$$B(t,z) = \int_t^\tau \int_0^z \frac{(s-t)G(t)}{g(\beta_0' w)G(s)} H_1(ds, dw).$$

Consider the martingale representation of the Kaplan-Meier estimator (Fleming and Harrington, 1991, p.97)

$$\frac{\hat{G}(t) - G(t)}{G(t)} = -\int_0^t \frac{\hat{G}(u-)}{G(u)} \frac{\sum_{i=1}^n M_i^c(u)}{n\pi_n(u)}, \qquad (A.8)$$

where $M_i^c(t) = N_i^c(t) - \int_0^t I(X_i \geq u) d\Lambda^c(u)$ and $\Lambda^c(t) = -\log(G(t))$ is the cumulative hazard function of the censoring times. It is well known that $M_i^c(t)$ $(i = 1, ..., n)$ are martingales with respect to the σ-filtration

$$\sigma\{I(X_i \geq u), I(X_i \leq u, \delta_i = 0), Z_i : 0 \leq u \leq t, i = 1, ..., n\}.$$

It follows from (A.8) and a Taylor series expansion that

$$B_n(t,z) - B(t,z) = n^{-1} \int_t^\tau \int_0^z \frac{(s-t)G(t)}{g(\beta_0' w)G(s)} \left(\int_t^s \frac{dM_i^c(u)}{\pi(u)}\right) H_1(ds, dw)$$
$$+ \int_t^\tau \int_0^z \frac{(s-t)G(t)}{g(\beta_0' w)G(s)} [H_{1n}(ds, dw) - H_1(ds, dw)]$$

$$-\int_t^\tau\int_0^z \frac{(s-t)h(\beta_0'w)w'G(t)}{g(\beta_0'w)G(s)}H_1(ds,dw)(\hat\beta_a-\beta_0)+o_p(1). \qquad (A.9)$$

Thus, combining (A.5), (A.7) and (A.9), we have

$$\theta_n(t,z)=\phi_n(t,z)-\phi_n(t,z_u)=n^{-1/2}\sum_{i=1}^n \eta_i(t,z)+o_p(1),$$

where $\eta_i(t,z)=\rho_i(t,z)-\rho_i(t,z_u)$, and

$$\begin{aligned}\rho_i(t,z)=&\frac{G(t)}{H(t,z)}\int_t^\tau\left[\int_u^\tau\int_0^z\frac{s-t}{G(s)g(\beta_0'w)}H_1(ds,dw)\right]\frac{dM_i^c(u)}{\pi(u)}\\&+\frac{\delta_i(X_i-t)G(t)}{H(t,z)G(X_i)g(\beta_0'Z_i)}I(X_i\ge t,Z_i\le z)-\frac{V(t,z)}{H(t,z)}I(X_i\ge t,Z_i\le z)\\&+\frac{G(t)}{H(t,z)}\int_t^\tau\int_0^z\frac{(s-t)h(\beta_0'w)w'}{g(\beta_0'w)G(s)}H_1(ds,dw)\\&\times A^{-1}\int_0^\tau\{h(\beta_0'Z_i)Z_i-\mu(u)\}\,m_0(u)dM_i(u).\end{aligned}$$

Thus, by the same arguments as those of Appendix A.5 in Lin et al. (2000), $\theta_n(t,z)$ converges weakly to zero-mean Gaussian process with covariance function $\sigma(t,z;t^*,z^*)=E\{\eta_i(t,z)\eta_i(t^*,z^*)\}$ at (t,z) and (t^*,z^*), which can be consistently estimated by $\hat\sigma(t,z;t^*,z^*)$ given in Section 4.

REFERENCES

Cai, J., Schaubel, D. E. (2004). Marginal mean/rates models for multiple type recurrent event data. *Lifetime Data Analysis*, **10**, 121-138.

Chen, Y. Q. (2007). Additive Regression of Expectancy. *Journal of the American Statistical Association*, **102**, 153-166.

Chen, Y. Q., Jewell, N. P., Lei, X., Cheng, S. C. (2005). Semiparametric estimation of proportional mean residual life model in presence of censoring. *Biometrics*, **61**, 170-178.

Chen, Y. Q., Cheng, S. C. (2005). Semiparametric regression analysis of mean residual life with censored survival data. *Biometrika*, **92**, 19-29.

Chen, Y. Q. and Cheng, S. C. (2006). Linear Life Expectancy Regression with Censored Data. *Biometrika*, **93**, 303-13.

Cox, D. R. (1962). *Renewal Theory.* London: Spottiswoode Ballantyne.

Cox, D. R. (1972). Regression Models and Life-Tables (with Discussion). *Journal of the Royal Statistical Society*, Ser. B, **34**, 187-220.

Fleming, T. R., Harrington, D. P. (1991). *Counting processes and survival analysis.* New York: John Wiley.

Lad, T., Rubinstein, L, and Sadeghi, A. (1988). The benefit of adjuvant treatment for resected locally advanced non-small-cell lung cancer. *Journal of Clinical Oncology*, **6**, 9-17.

Liang, K. Y., Zeger, S. L. (1986). Longitudinal data analysis using generalized linear models. *Biometrika*, **73**, 13-22.

Lin, D. Y., Wei, L. J., Yang, I. and Ying, Z. (2000). Semiparametric Regression for the Mean and Rate Functions of Recurrent Events. *Journal of the Royal Statistical Society*, Ser. B, **62**, 711-730.

Lin, D. Y., Wei, L. J. and Ying, Z. (2001). Semiparametric Transformation Models for Point Processes. *Journal of the American Statistical Association*, **96**, 620-628.

Maguluri, G. and Zhang, C.-H. (1994). Estimation in the Mean Residual Life Regression Model. *Journal of the Royal Statistical Society*, Ser. B, **56**, 477-489.

Oakes, D., Dasu, T. (1990). A note on residual life. *Biometrika*, **77**, 409-410.

Piantadosi, S. (2005). *Clinical Trials: A Methodologic Perspective*, 2nd Edition. New York: John Wiley.

Prentice, R. L., Self, S. G. (1983). Asymptotic distribution theory for Cox-type regression models with general relative risk form. *The Annals of Statistics*, **11**, 804-813.

Pollard, D. (1990). *Empirical Processes: Theory and Applications.* Hayward, CA: Institute of Mathematical Statistics.

Robins, J. M., Rotnitzky, A. (1992). Recovery of information and adjustment for dependent censoring using surrogate markers. In *AIDS Epidemiology-Methodologic Issues,* eds. N. Jewell, K. Dietz, and V. Farewell, Boston: Birkhauser, 24-33.

Yuen, K. C., Zhu, L. X., Tang, N. Y. (2003). On the mean residual life regression model. *Journal of Statistical Planning and Inference*, **113**, 685–698.

Table 1: Simulation Results (Independent Censoring)

			$g_1(x) = 1 + x$				$g_2(x) = e^x$				$g_3(x) = \log(1 + e^x)$			
n	β_0	p	$\bar{\hat{\beta}}_a$	SE	SEE	CP	$\bar{\hat{\beta}}_a$	SE	SEE	CP	$\bar{\hat{\beta}}_a$	SE	SEE	CP
100	0.0	10%	0.0047	0.1225	0.1220	0.945	-0.0022	0.1229	0.1215	0.943	-0.0018	0.1961	0.2061	0.968
100	0.0	30%	0.0044	0.1368	0.1360	0.945	-0.0048	0.1364	0.1354	0.953	0.0010	0.2142	0.2322	0.976
100	0.5	10%	0.5044	0.1505	0.1531	0.943	0.4998	0.0960	0.0962	0.948	0.5056	0.2009	0.2139	0.970
100	0.5	30%	0.5053	0.1653	0.1684	0.952	0.4985	0.1072	0.1054	0.945	0.5060	0.2193	0.2393	0.974
200	0.0	10%	0.0014	0.0855	0.0856	0.943	-0.0022	0.0853	0.0855	0.947	-0.0025	0.1420	0.1444	0.952
200	0.0	30%	0.0031	0.0952	0.0955	0.949	-0.0014	0.0947	0.0952	0.953	-0.0009	0.1600	0.1625	0.951
200	0.5	10%	0.5030	0.1080	0.1079	0.948	0.4990	0.0681	0.0680	0.957	0.5020	0.1480	0.1499	0.950
200	0.5	30%	0.5030	0.1180	0.1186	0.948	0.4980	0.0742	0.0744	0.951	0.5030	0.1650	0.1675	0.957

p represents proportion of right-censoring; $\bar{\hat{\beta}}_a$ represents the mean of the point estimates of β_0; SE represents sample standard error of $\hat{\beta}_a$; SEE represents the mean of the standard error of $\hat{\beta}_a$; CP represents the empirical 95% coverage probability.

Table 2: Simulation Results (Dependent Censoring)

			$g_1(x) = 1 + x$				$g_2(x) = e^x$				$g_3(x) = \log(1 + e^x)$			
n	β_0	p	$\bar{\hat{\beta}}_b$	SE	SEE	CP	$\bar{\hat{\beta}}_b$	SE	SEE	CP	$\bar{\hat{\beta}}_b$	SE	SEE	CP
100	0.0	10%	-0.0015	0.1111	0.1153	0.948	-0.0110	0.1113	0.1155	0.957	-0.0176	0.1934	0.2013	0.954
100	0.0	30%	-0.0051	0.1427	0.1458	0.936	-0.0156	0.1379	0.1460	0.955	-0.0452	0.2307	0.2562	0.955
100	0.5	10%	0.5032	0.1340	0.1453	0.966	0.5017	0.0875	0.0922	0.956	0.4948	0.1928	0.2048	0.966
100	0.5	30%	0.5066	0.1561	0.1855	0.978	0.5096	0.09804	0.1189	0.983	0.4829	0.2187	0.2591	0.985
200	0.0	10%	0.0009	0.0793	0.0814	0.954	-0.0029	0.0799	0.0814	0.959	-0.0087	0.1412	0.1432	0.945
200	0.0	30%	-0.0077	0.0967	0.1024	0.956	-0.0122	0.0964	0.1030	0.961	-0.0461	0.1743	0.1845	0.947
200	0.5	10%	0.5079	0.0968	0.1028	0.962	0.5024	0.0597	0.0653	0.959	0.4997	0.1407	0.1457	0.957
200	0.5	30%	0.5099	0.1083	0.1296	0.987	0.5102	0.0652	0.0831	0.991	0.4745	0.1659	0.1827	0.966

p represents proportion of right-censoring; $\bar{\hat{\beta}}_b$ represents the mean of the point estimates of β_0; SE represents sample standard error of $\hat{\beta}_b$; SEE represents the mean of the standard error of $\hat{\beta}_b$; CP represents the empirical 95% coverage probability.

Table 3: Estimation of the effects for the lung cancer data

Covariates	$g(x)$	Parameter estimate	SEE	p-value
	$1+x$	1.2249	0.6130	0.0457
Treatment (Z_1)	e^x	0.7334	0.2413	0.0024
	$\log(1+e^x)$	1.2487	0.5164	0.0156
	$1+x$	1.0596	0.6338	0.0946
Cell type (Z_2)	e^x	0.6528	0.2590	0.0117
	$\log(1+e^x)$	1.1035	0.5462	0.0434

Note: SEE is the standard error estimate; p-value pertains to testing no covariate effect.

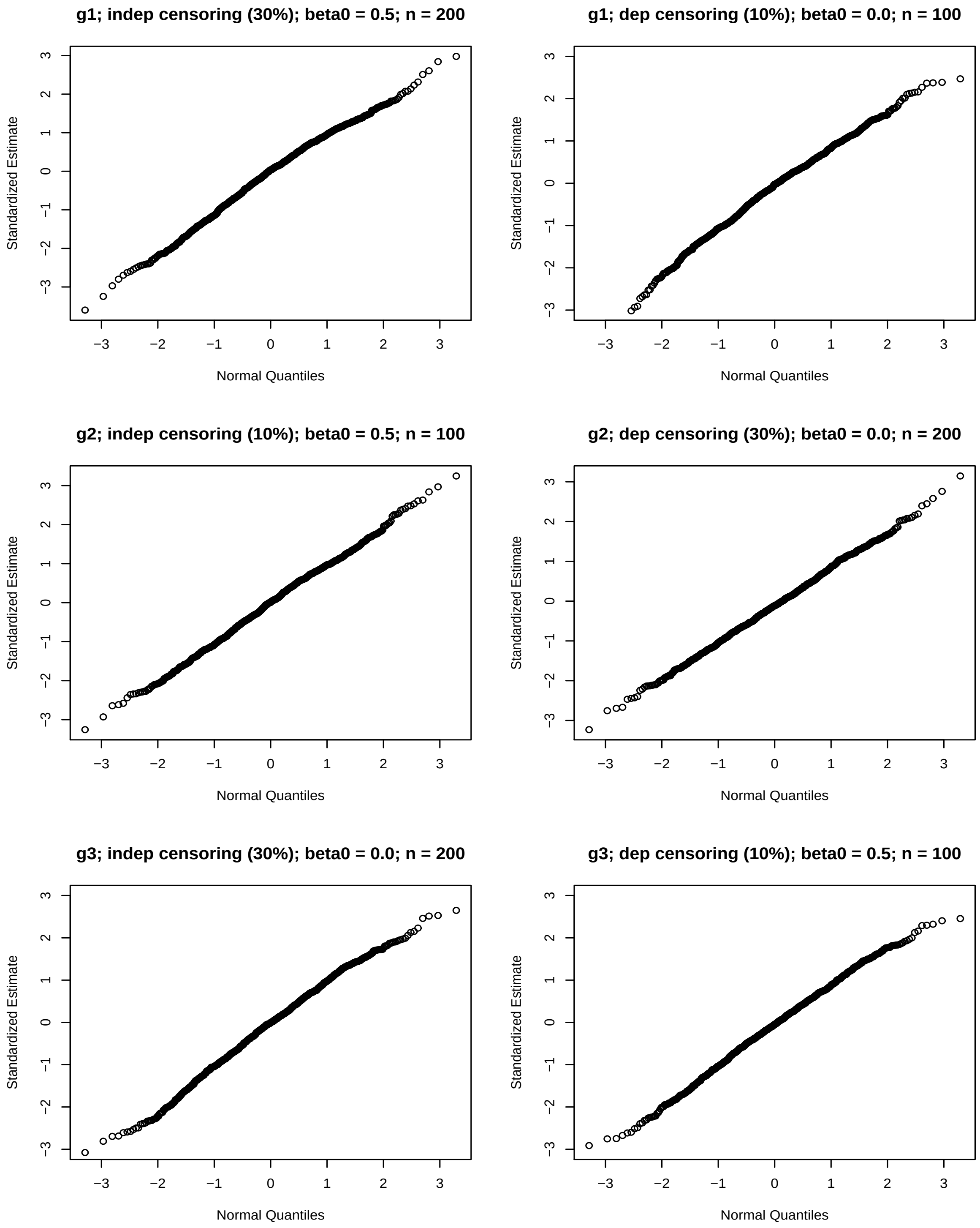

Figure 1: Normal Q-Q Plots

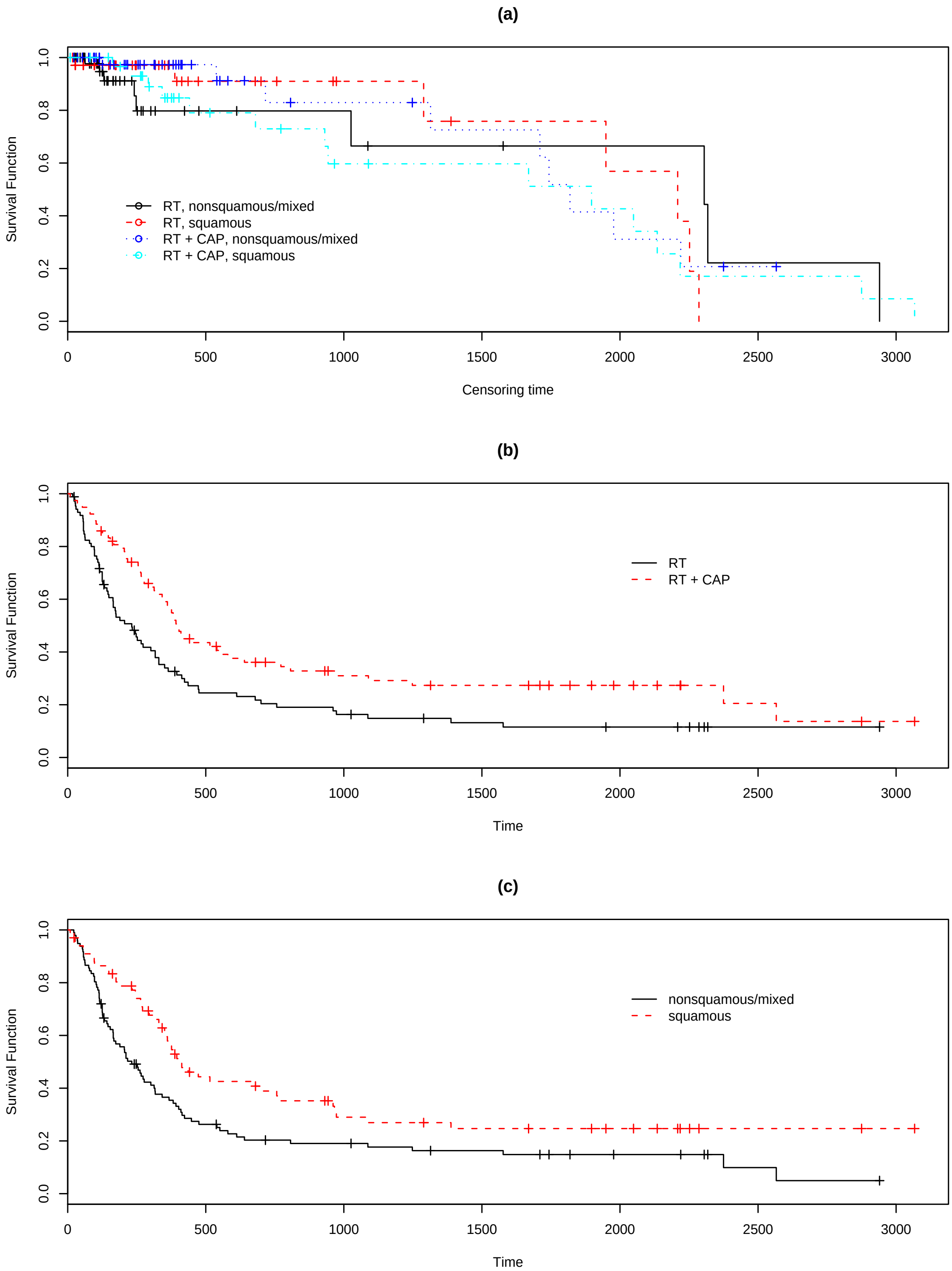

Figure 2: Kaplan-Meier Estimates of Survival Functions