Proportional Mean Residual Life Model with Censored Survival Data under Case-cohort Design *

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August 8, 2017

Abstract: Proportional mean residual life model is studied for analysing survival data from the case-cohort design. To simultaneously estimate the regression parameters and the baseline mean residual life function, weighted estimating equations based on an inverse selection probability are proposed. The resulting regression coefficients estimates are shown to be consistent and asymptotic normal with easily estimated variance-covariance. Simulation studies show that the proposed estimators perform very well. An application to a real dataset from the South Welsh nickel refiners study is also given to illustrate the methodology.

Keywords: Censored survival data; Estimating equation; Mean residual life; Case-cohort design

1 Introduction

When studying the natural history of an event, such as the fields of survival analysis, medical study, actuarial science and reliability research, the residual lifetime is often regarded as a crucial index for investigators to make decisions. The mean residual life function (MRLF) is one of the most important quantitative measures for the residual lifetimes that can describe the characteristics of the residual life time more directly. The MRLF for a nonnegative
survival time $T$ with finite expectation at time $t \geq 0$ is defined as $m(t) = \mathbb{E}(T - t | T > t)$. It is often of interest to analyse the mean residual life function in many applications. For example, a driver may be interested in knowing how much longer his or her car can be used, given that the car has worked normally for $t$ years. Many early literatures on MRLF studied its probability behaviours, statistical inference on testing procedures and the estimation in homogeneous cases. Apparently, the MRLF may vary due to different covariates. To quantify and summarize the association between the MRLF and its associated covariates, extensive regression models are explored. Oakes and Dasu (1990) originally proposed the proportional mean residual life model, which has been studied by many authors later. The proportional mean residual life model, or the Oakes–Dasu model, is specified by

$$m(t|Z) = m_0(t) \exp(\beta^\top Z),$$

where $m(t|Z)$ is the mean residual life with the $p$-vector covariate $Z$, $\beta$ is the usual regression $p$-parameter vector, and $m_0(t)$ is an unknown baseline mean residual life. Maguluri and Zhang (1994) developed estimation procedures for regression coefficients mainly for uncensored survival data, which was later modified to accommodate right censoring setting in Chen et al. (2005). Chen and Cheng (2005) used counting process theory to develop another semiparametric inference procedures for the proportional mean residual life model. Chen and Cheng (2006) and Chen (2007) proposed the additive mean residual life model and discussed various estimation methodologies with or without right censoring. Sun and Zhang (2009) proposed a more general family of transformed mean residual life model, including the proportional mean residual life model and the additive mean residual life model as special cases.

However, the above methods for mean residual life models are not suitable when some covariates are missing. In large cohort studies, the major effort and cost arise from the assembling and analysing of covariate measurement. When the disease rate is low, assembling all covariates for every subject may become redundant and expensive. Prentice (1986) proposed case-cohort design to provide a cost effective way of conducting such cohort studies. Under this design, a random sample from the entire cohort is selected, named the subcohort. Covariate information is collected only for the subjects in the subcohort and all the cases who experience the event of interest. After the landmark article of Prentice (1986), the case-cohort design has been extensively studied in many statistical literatures. Standard analysis of the case-cohort design are conducted using the Cox proportional hazards model (Cox, 1972). For example, a pseudo-likelihood procedure proposed by Prentice (1986) was later elaborated by Self and Prentice (1988) and Lin and Ying (1993). Several other au-
thors studied other regression models such as the additive hazards model (Kulich and Lin, 2000), the proportional odds model (Chen, 2001b) and the semiparametric transformation regression model (Chen, 2001a; Kong et al., 2004; Lu and Tsiatis, 2006; Chen and Zucker, 2009). Borgan et al. (2000), Kulich and Lin (2004) and Breslow and Wellner (2007) among others, extended the classical case-cohort design to more complex sampling schemes. Besides, Zheng et al. (2013) conducted quantile regression analysis of case-cohort data. All these models may be adopted to indirectly make statistical inference for the mean residual lifetime. But they are relatively cumbersome and not straightforward to measure the residual life. Further, one drawback about the hazard function is its interpretation as “instantaneous rate of failure”, which is conceptually difficult to understand for practical use. Consequently, improving statistical methods for mean residual life models are needed under the case-cohort design.

Just as mentioned before, existing methods for mean residual life models are used for cohort data with complete covariate information, they are not suitable for the case-cohort data. To the best of our knowledge, there have been no study about mean residual life model under case-cohort design. In this paper, we focus on proportional mean residual life model for the analysis of case-cohort data. Our research is initially motivated by a nickel refiners study in the South Welsh where the refiners are interested in knowing how long they can still survive given his current situation. Thus, the mean residual life model is an informative choice. Further, the event rate for this study is quite low and hence the case-cohort design is preferred. Our approach is motivated by Chen and Cheng (2005), who made use of the counting process theory in constructing some estimating equations and does not require estimating or modelling the distribution of censoring. The main difficulty here is that some covariates are missing and the subjects whether they should be selected in the subcohort are not independent with each other.

The remainder of this paper is organized as follows. In Section 2, several new weighted estimating equations are proposed for simultaneous estimation of the regression parameters and the baseline mean residual life function. Some large sample properties of the resulting regression coefficients estimates are also given in this section. Section 3 is devoted to simulation studies to examine the finite sample properties of the regression parameter estimators. In Section 4, a real dataset from the South Welsh nickel refiners study is used to illustrate the proposed estimating procedures. Section 5 contains some concluding remarks and the outline of the proofs is provided in the Appendix finally.
2 Estimating Equations and Theoretical Results

The failure time and potential censoring time are denoted as $T$ and $C$, respectively, which are assumed to be independent given the $p \times 1$ covariate vector $Z$. Let $\bar{T} = \min(T, C)$ and $\delta = I(T \leq C)$, then the usual counting process and the at-risk process at time $t$ can be defined as $N(t) = \delta I(\bar{T} \leq t)$ and $Y(t) = I(\bar{T} \geq t)$, respectively. Complete data on a sample of $n$ individuals are modeled as $n$ independent and identically distributed random vectors $(\tilde{T}_i, \delta_i, Z_i)$, where $\tilde{T}_i = \min(T_i, C_i)$ and $\delta_i = I(T_i \leq C_i)$ for $i = 1, 2, \ldots, n$. Consider the filtration defined by $\mathcal{F}_i = \sigma\{N_i(u), Y_i(u), Z_i : 0 \leq u \leq t, i = 1, 2, \ldots, n\}$, then $M_i(t; \beta_*, m_*) = N_i(t) - \int_0^t Y_i(s) d\Lambda_i(s; \beta_*, m_*)$ are martingales with respect to $\mathcal{F}_i$, where $\Lambda_i(\cdot)$ denotes the usual cumulative hazard function for subject $i$, $\beta_*$ and $m_*(\cdot)$ are the true values of $\beta$ and $m_0(\cdot)$, respectively. The martingale properties of $M_i(\cdot)$ implies $\mathbb{E}[dM_i(t; \beta_*, m_*)] = 0$ for $i = 1, \ldots, n$. Furthermore,

$$
\mathbb{E}[m_*(t)dM_i(t; \beta_*, m_*)] = \mathbb{E}[m_*(t)dN_i(t) - m_*(t)Y_i(t)d\Lambda_i(t; \beta_*, m_*)] = \mathbb{E}[m_*(t)dN_i(t) - Y_i(t)\{\exp(-\beta_*^T Z_i)dt + dm_*(t)\}] = 0. \quad (2)
$$

For simplicity, we assume that $0 < \tau = \inf\{t : \Pr(\bar{T} > t) = 0\} < \infty$. When the gathered data was complete, Chen and Cheng (2003) proposed the following two estimating equations to estimate $(\beta_*, m_*(t))$:

$$
\sum_{i=1}^n \{m_0(t)dN_i(t) - Y_i(t)\{\exp(-\beta^T Z_i)dt + dm_0(t)\}\} = 0 \quad (0 \leq t \leq \tau), \quad (3)
$$

$$
\sum_{i=1}^n \int_0^\tau Z_i \{m_0(t)dN_i(t) - Y_i(t)\{\exp(-\beta^T Z_i)dt + dm_0(t)\}\} = 0. \quad (4)
$$

Under the case-cohort design, since $Z_i$ is not observed for all subjects, the estimating equations (3) and (4) based on the entire cohort data are no longer available. In this paper, we assume that the subcohort with fixed size $\tilde{n}$ is drawn from the entire cohort by the simple random sampling. Let $\xi_i$ be the subcohort indicator, taking the value 1 or 0, whether the subject is included in the subcohort or not. Hence the data can be summarised as $\{(\tilde{T}_i, \delta_i, \xi_i, (1 - \delta_i)\xi_i Z_i), i = 1, 2, \ldots, n\}$, which means that $(\tilde{T}_i, \delta_i)$ are available for all individuals in the entire cohort, and $Z_i$ only for subjects in the subcohort with $\xi_i = 1$, and all the cases outside the subcohort with $\delta_i = 1$ and $\xi_i = 0$. Here $\xi_i$ is independent of $(\tilde{T}_i, \delta_i, Z_i), i = 1, 2, \ldots, n$, while the $\xi_i$s are dependent because of the sampling without replacement. Similar to Kong et al. (2004) and Lu and Tsiatis (2006), for each individual in
the full cohort, we define a weight \( \pi_i = \delta_i + (1 - \delta_i)\xi_i/\hat{p} \) by the idea of the inverse selection probabilities, where \( \hat{p} = \frac{n}{n} \).

Now we propose the estimator by two steps in the following.

First, we develop a new estimator for \( m_0(t) \) as if the true regression coefficients \( \beta \) have been known. We propose the estimating equation by incorporating the weight \( \pi_i, \)

\[
\sum_{i=1}^{n} \pi_i \left[ m_0(t) dN_i(t) - Y_i(t) \left\{ \exp(-\beta^T Z_i) dt + dm_0(t) \right\} \right] = 0
\]

\[
\iff \left\{ \sum_{i=1}^{n} \pi_i dN_i(t) \right\} m_0(t) - dm_0(t) = \frac{\sum_{i=1}^{n} \pi_i Y_i(t) \exp(-\beta^T Z_i)}{\sum_{i=1}^{n} \pi_i Y_i(t)} dt.
\]

Equation (6) is in fact a first-order linear ordinary differential equation about \( m_0(t) \), which possesses a closed form solution

\[
\hat{m}_0(t) \overset{\Delta}{=} \hat{m}_0(t; \beta) = \frac{1}{S_n(t)} \int_{t}^{\tau} S_n(u) B_n(u; \beta) du,
\]

where

\[
S_n(t) = \exp \left\{ - \int_{0}^{t} \frac{\sum_{i=1}^{n} \pi_i dN_i(u)}{\sum_{i=1}^{n} \pi_i Y_i(u)} \right\}
\]

and

\[
B_n(t; \beta) = \frac{\sum_{i=1}^{n} \pi_i Y_i(t) \exp(-\beta^T Z_i)}{\sum_{i=1}^{n} \pi_i Y_i(t)}.
\]

Based on the mean-zero process \( N_i(t) - \int_{0}^{t} \pi_i Y_i(u) d\Lambda_i(u; \beta_*, m_*) \), it is easy to show that \( S_n(t) \) is a consistent estimator of the survival function for the failure time \( T \).

Next, we propose the estimating equations to estimate \( \beta_* \). Define

\[
U\{\beta, m_0(\cdot)\} = \frac{1}{n} \sum_{i=1}^{n} \int_{0}^{\tau} \pi_i Z_i \left[ m_0(t) dN_i(t) - Y_i(t) \left\{ \exp(-\beta^T Z_i) dt + dm_0(t) \right\} \right].
\]

Note that

\[
U\{\beta_*, m_*(\cdot)\} = \frac{1}{n} \sum_{i=1}^{n} \int_{0}^{\tau} \pi_i Z_i \left[ m_*(t) dN_i(t) - Y_i(t) \left\{ \exp(-\beta_*^T Z_i) dt + dm_*(t) \right\} \right]
\]

\[
= \frac{1}{n} \sum_{i=1}^{n} \int_{0}^{\tau} \pi_i Z_i m_*(t) dM_i(t; \beta_*, m_*)
\]

are mean-zero. To obtain a consistent estimator for \( \beta_* \), we replace \( m_0(t) \) with \( \hat{m}_0(t; \beta) \) in \( U\{\beta, m_0(\cdot)\} \), and define \( Z(t) = \frac{\sum_{i=1}^{n} \pi_i Z_i Y_i(t)}{\sum_{i=1}^{n} \pi_i Y_i(t)} \), then the resulting equation is equivalent to

\[
U(\beta) \overset{\Delta}{=} U(\beta, \hat{m}_0(t; \beta))
\]
\[
\frac{1}{n} \sum_{i=1}^{n} \int_0^\tau \pi_i \{Z_i - \bar{Z}(t)\} \{\hat{m}_0(t; \beta) dN_i(t) - Y_i(t) \exp(-\beta^T Z_i) dt\} = 0. \quad (11)
\]

The resulting estimator is denoted by \( \hat{\beta} \), which has several good properties such as consistency and asymptotic normality.

In order to derive the large sample properties of \( \hat{\beta} \), some notations and regularity conditions are needed. Denote
\[
\frac{\hat{m}_0(t; \beta) dN_i(t) - Y_i(t) \exp(-\beta^T Z_i) dt}{n^{-1} \sum_{i=1}^{n} \pi_i Y_i(t)} = 0.
\]
and let \( \mu_z(t) \) and \( \tilde{\mu}_z(t) \) be the limits of \( \bar{Z}(t) \) and \( \tilde{Z}(t) \), respectively.

We give the following regularity conditions:

C1 sup supp(F) \leq sup supp(G), where \( F(\cdot) \) and \( G(\cdot) \) are the distribution functions of \( T \) and \( C \), respectively;

C2 \( \sup_i \|Z_i\| < \infty \), where \( \|u\| \) denote the Euclidean norm of vector variable \( u \);

C3 \( m_*(t) \) is continuously differentiable on \([0, \tau]\);

C4 \( A = \int_0^\tau E \left\{ \{Z - \mu_z(t)\} \otimes^2 \exp(-\beta^T Z) H(t|Z) \right\} dt \) is nonsingular, where \( a \otimes^2 \) denotes \( aa^T \) for a vector \( a \).

C5 \( \tilde{n}/n \) converges to \( p \) as \( n \to \infty \), where \( p_0 \leq p \leq 1 \) for some \( p_0 > 0 \).

Condition C1 is imposed to ensure that the mean residual life function is estimable, otherwise the MRLF of \( T \) may not be estimable at some points. From the technical arguments, this assumption also saves us from lengthy technical discussion of the tail behavior of the limiting distributions. Such an assumption has been adopted by other investigators in regression analysis of the mean residual life function, see, for example, Chen and Cheng (2003), Chen et al. (2005), Chen and Cheng (2006) and Sun and Zhang (2009). This assumption may not hold if the survival time has an extremely long tail. It may also fail when the follow-up period is too short or when the tail is subject to administrative censoring. However, in well-designed clinical studies with a nonzero event rate and long follow-up, this assumption is reasonable.

For introduce our results, let
\[
\Sigma = \Sigma_1 + \Sigma_2,
\]
\[
\Sigma_1 = E \left[ \int_0^\tau \{Z_1 - \mu_z(t) - \tilde{\mu}_z(t)\} m_*(t) dM_1(t) \right] \otimes^2,
\]

Theorem 1. Suppose conditions C1–C5 hold, then
(i) $\hat{\beta}$ and $\hat{m}_0(t)$ always exist and are consistent.
(ii) $n^{1/2}(\hat{\beta} - \beta_*)$ is asymptotic normal with mean zero and a variance-covariance matrix $A^{-1}\Sigma(A^{-1})^\top$. Moreover, $A$ and $\Sigma$ can be consistently estimated by $\hat{A}$ and $\hat{\Sigma}$ respectively, where

$$
\hat{A} = \frac{1}{n} \sum_{i=1}^n \pi_i \int_0^\tau \{Z_i - \bar{Z}(t)\}^\top Y_i(t) \exp(-\hat{\beta}^\top Z_i) dt,
$$

$$
\hat{\Sigma} = \hat{\Sigma}_1 + \hat{\Sigma}_2,
$$

$$
\hat{\Sigma}_1 = \frac{1}{n} \sum_{i=1}^n \pi_i \int_0^\tau \{Z_i - \bar{Z}(t)\}^2 Y_i(t) \exp(-\hat{\beta}^\top Z_i) dt \mathbb{I}(\exp(-\hat{\beta}^\top Z_i) dt),
$$

$$
\hat{\Sigma}_2 = \frac{1}{\hat{p}} \sum_{i=1}^n \left[ \int_0^\tau (1 - \delta_i) \frac{\xi_i}{\hat{p}} \left\{Z_i - \bar{Z}(t)\right\} \hat{m}_0(t; \beta) \mathbb{I}(\exp(-\hat{\beta}^\top Z_i) dt + d\hat{m}_0(t; \beta)) \right]^2 dt,
$$

$$
- \frac{1}{\hat{p}} \left( \frac{1}{n} \sum_{i=1}^n \left[ \int_0^\tau (1 - \delta_i) \frac{\xi_i}{\hat{p}} \left\{Z_i - \bar{Z}(t)\right\} \hat{m}_0(t; \beta) d\hat{M}_i(t) \right]^2 \right).
$$

(iii) $n^{1/2}\{\hat{m}_0(t) - m_*(t)\}(0 \leq t \leq \tau)$ converges weakly to a mean zero Gaussian process with the covariance function that will be given in the Appendix.

The proof of Theorem 1 is given in the Appendix.

Although $\hat{\beta}$ has properties such as consistency and asymptotic normality that can be used to make valid inferences about $\beta_*$, the ad hoc nature of $U(\beta)$ would not lead to efficient estimators, however. Note that equation (11) is constructed via the method of moments, one of the shortcomings for the method of moments is that it may not necessarily be efficient. To improve the efficiency, we explore the following approaches via two aspects.

One is that by adding proper weight functions. The following weighted version of the estimating equations can be used to estimate $\beta_*:

$$
\frac{1}{n} \sum_{i=1}^n \int_0^\tau \pi_i W_i(t) \{Z_i - \bar{Z}(t)\} \{\hat{m}_0(t; \beta) dN_i(t) - Y_i(t) \exp(-\hat{\beta}^\top Z_i) dt\} = 0, \tag{12}
$$

where $W_i(t)$ is a possibly data-dependent and $\mathcal{F}_t$–measurable weight function which converges uniformly to some deterministic function $w(t)$ almost surely. Denote the solution to the equation (12) as $\hat{\beta}_w$, by using the technique in the Appendix, $\hat{\beta}_w$ is shown to be consistent.
and asymptotically normal with asymptotic variance $n^{-1}A^{-1}_w \Sigma_w A^{-1}_w$, where

$$A_w = \int_0^\tau E \left[ w(t) \{Z - \mu_z(t)\} \otimes^2 \exp(-\beta^T_i Z)H(t|Z) \right] dt,$$

$$\Sigma_w = \Sigma_{w1} + \Sigma_{w2},$$

$$\Sigma_{w1} = E \left[ \int_0^\tau w(t) \{Z_1 - \mu_z(t) - \tilde{\mu}_z(t)\} m_s(t) dM_1(t) \right]^\otimes^2,$$

$$\Sigma_{w2} = \frac{1-p}{p} E \left[ \int_0^\tau w(t)(1-\delta_1) \{Z_1 - \mu_z(t) - \tilde{\mu}_z(t)\} m_s(t) dM_1(t) \right]^\otimes^2,$$

$$-\frac{1-p}{p} \left( E \left[ \int_0^\tau w(t)(1-\delta_1) \{Z_1 - \mu_z(t) - \tilde{\mu}_z(t)\} m_s(t) dM_1(t) \right] \right)^\otimes^2.$$

Chen and Cheng (2005) has used the Cauchy–Schwarz inequality to prove that

$$W_i(t) = \frac{\exp(-\beta^T_i Z_i)}{\hat{m}_0(t)\{\exp(-\beta^T_i Z_i) + \hat{m}_0'(t)\}},$$

(13)

can improve the estimation efficiency. So we also suggest this choice of $W_i(t)$, which actually decrease the estimated variance in our simulation results.

The other is through the stratified case-cohort design. If an individual characteristics $Z^*$ being highly correlated with $Z$ is available for all the subjects in the cohort, Nan et al. (2004) suggested that selecting the subcohort using stratified sampling based on $Z^*$ can improve efficiency in hazard regression models. We expect that a similar result holds for mean residual life models, which have been supported by the simulation studies in next section. Many sampling schemes can be designed for selecting a stratified subcohort. In this paper, we allow $\xi_i$ to depend on $Z^*_i$, which may involve $\tilde{T}_i, Z_i$ and some external variables correlated with $\tilde{T}_i$ and $Z_i$, and the $\xi'_i$s are independent Bernoulli variables with possibly unequal success probabilities. Let $p_i = \Pr(\xi_i = 1) = p(Z_i^*)$, where $p(Z_i^*)$ is a function mapping the sample space of $Z^*$ to $(p_0, 1)$ for some $p_0 > 0$. Although the size of the subcohort $\tilde{n} = \sum_{i=1}^n \xi_i$ is random, if $\frac{1}{n} \sum_{i=1}^n p_i$ converges to the limiting subcohort proportion $p \in (0, 1]$ in probability, then also does $\tilde{n}/n$.

Note that when there is only a single stratum, the independent Bernoulli sampling proposed for selecting the subcohort in the stratified case-cohort design does not reduce to sampling without replacement. The stratified case-cohort design keeps the independent structure while the classical case-cohort study does not, which results in the different proofs of their asymptotic properties. In fact, similar to the technique used in the Appendix of Kulich and Lin (2000), we can prove that this resulting estimator $\hat{\beta}_s$ is a consistent and asymptotically normal estimator of $\beta_s$, the asymptotic variance of $\hat{\beta}_s$ is $A^{-1} \Sigma_s (A^{-1})^\top$, where $\Sigma_s = \Sigma_{s1} + \Sigma_{s2}$.
with
\[
\Sigma_{s1} = E \left[ \int_0^\tau \{ Z_1 - \mu_z(t) - \tilde{\mu}_z(t) \} m_*(t) dM_1(t) \right]^2 ,
\]
\[
\Sigma_{s2} = \frac{1 - p}{p} E \left[ \int_0^\tau (1 - \delta) \{ Z_1 - \mu_z(t) - \tilde{\mu}_z(t) \} m_*(t) dM_1(t) \right]^2 .
\]

3 Simulation Studies

In this Section, we conduct simulation studies to examine the finite sample properties of the proposed estimating estimator.

In the first scenario of simulation studies, the event time \( T \) is generated from the following proportional mean residual life regression model
\[
m(t|Z) = m_0(t) \exp(\beta_1 Z_1 + \beta_2 Z_2),
\]
where the covariate \( Z_1 \) is a Bernoulli random variable with success probability 0.5, \( Z_2 \) is a \( U(0,1) \) variable, the true regression parameters \( (\beta_1^*, \beta_2^*)^\top \) is respectively set to be \( (0, 0)^\top \), \( (0.2, 0.2)^\top \) or \( (0.5, -0.5)^\top \) and the baseline function \( m_0(t) \) is taken from the Hall-Wellner family, in other words, \( m_0(t) = (D_1 t + D_2)^+ \), where \( D_1 > -1, \ D_2 > 0, \) and \( d^+ \) denotes \( d \cdot I(d \geq 0) \) for any quantity \( d \). Here we consider two scenarios for the baseline function \( m_0(t) \). One is that \( D_1 = -0.5 \) and \( D_2 = 0.5 \), the other is under \( D_1 = -0.5 \) and \( D_2 = 1 \). The censoring time \( C \) is generated from \( \text{Exp}(\lambda) \), where \( \lambda \) is used to control the censoring proportion. We set the censoring rate to be 70% or 80% to mimic the low event rate where the case-cohort designs are more adopt to be applied. Care is taken to ensure that the support of \( C \) is larger than the support of \( T \) for all \( Z \).

500 replications of full cohort data are generated with the sample size \( n = 1000 \). For each replication, subcohort of size 200 and size 300 are drawn by simple random sampling, respectively. The empirical biases (Bias), empirical standard deviations (SD), average robust standard errors (SE), coverage probabilities of the 95% confidence intervals (CP) and the empirical relative efficiency (RE) of the proposed \( \hat{\beta} \) are reported in the study. We also report the estimation and inference results based on full cohort for comparison. The simulation results are summarized in Table 1 and Table 2 when the censoring rates are approximately 70% and 80%, respectively.

It can be seen from the simulation results in Table 1 and Table 2 that the proposed estimates are all essentially unbiased under two different subcohorts. The means of estimated standard errors match the empirical standard errors quite well and the 95% confidence in-
Table 1: Simulation results when the censoring rate is approximately 70%

|                  | Full          | Subcohort:200 | Subcohort:300 |
|------------------|---------------|---------------|---------------|
|                  | $\beta_1$    | $\beta_2$    | $\beta_1$    | $\beta_2$    | $\beta_1$    | $\beta_2$    |
| $m_0(t) = (-0.5t + 0.5)^+, \beta = (0, 0)^T$ | $m_0(t) = (-0.5t + 0.5)^+, \beta = (0, 0)^T$ | $m_0(t) = (-0.5t + 0.5)^+, \beta = (0, 0)^T$ | $m_0(t) = (-0.5t + 0.5)^+, \beta = (0, 0)^T$ |
| **BIAS**         | 0.005         | 0.001         | 0.004         | 0.007         | 0.006         | -0.001        |
| **SD**           | 0.057         | 0.100         | 0.097         | 0.148         | 0.083         | 0.138         |
| **SE**           | 0.060         | 0.104         | 0.088         | 0.153         | 0.079         | 0.137         |
| **CP**           | 94.8          | 96.0          | 91.6          | 94.4          | 93.8          | 94.2          |
| **RE**           | 1.00          | 1.00          | 0.35          | 0.46          | 0.48          | 0.53          |

|                  | $m_0(t) = (-0.5t + 0.5)^+, \beta = (0.2, 0.2)^T$ | $m_0(t) = (-0.5t + 0.5)^+, \beta = (0.5, -0.5)^T$ | $m_0(t) = (-0.5t + 1)^+, \beta = (0, 0)^T$ |
| **BIAS**         | 0.002         | -0.002        | 0.002         | -0.002        | 0.005         | 0.003         |
| **SD**           | 0.044         | 0.077         | 0.067         | 0.109         | 0.060         | 0.103         |
| **SE**           | 0.049         | 0.086         | 0.070         | 0.121         | 0.063         | 0.109         |
| **CP**           | 98.0          | 97.0          | 96.0          | 97.6          | 97.0          | 97.2          |
| **RE**           | 1.00          | 1.00          | 0.43          | 0.50          | 0.58          | 0.59          |

|                  | $m_0(t) = (-0.5t + 1)^+, \beta = (0.2, 0.2)^T$ | $m_0(t) = (-0.5t + 1)^+, \beta = (0.5, -0.5)^T$ | $m_0(t) = (-0.5t + 1)^+, \beta = (0, 0)^T$ |
| **BIAS**         | -0.003        | -0.001        | -0.004        | -0.003        | -0.002        | 0.001         |
| **SD**           | 0.046         | 0.081         | 0.068         | 0.114         | 0.058         | 0.145         |
| **SE**           | 0.049         | 0.086         | 0.069         | 0.120         | 0.064         | 0.146         |
| **CP**           | 96.2          | 97.0          | 96.2          | 96.0          | 96.4          | 95.4          |
| **RE**           | 1.00          | 1.00          | 0.47          | 0.50          | 0.54          | 0.31          |

BIAS, the empirical bias; SD, the empirical standard deviation; SE, the mean of estimated standard error; CP, the empirical coverage probability of 95% confidence interval; RE, the empirical relative efficiencies, calculated by the ratio of sample variance with the full estimators as a reference.
Table 2: Simulation results when the censoring rate is approximately 80%

|                  | Full         | Subcohort:200 | Subcohort:300 |
|------------------|--------------|---------------|---------------|
|                  | $\beta_1$    | $\beta_2$    | $\beta_1$    | $\beta_2$    | $\beta_1$    | $\beta_2$    |
| $m_0(t) = (-0.5t + 0.5)_+, \beta = (0, 0)^T$ |              |               |              |
| BIAS             | 0.003        | 0.003         | -0.003       | 0.010        | 0.006        | -0.012        |
| SD               | 0.066        | 0.118         | 0.104        | 0.186        | 0.093        | 0.171         |
| SE               | 0.073        | 0.127         | 0.105        | 0.182        | 0.095        | 0.165         |
| CP               | 97.2         | 96.8          | 94.8         | 93.0         | 96.8         | 94.6          |
| RE               | 1.00         | 1.00          | 0.40         | 0.40         | 0.50         | 0.48          |
| $m_0(t) = (-0.5t + 0.5)_+, \beta = (0.2, 0.2)^T$ |              |               |              |
| BIAS             | -0.004       | -0.004        | -0.007       | 0.003        | -0.005       | -0.008        |
| SD               | 0.054        | 0.098         | 0.079        | 0.139        | 0.071        | 0.129         |
| SE               | 0.059        | 0.102         | 0.083        | 0.143        | 0.075        | 0.129         |
| CP               | 97.2         | 96.0          | 95.8         | 95.8         | 95.6         | 93.6          |
| RE               | 1.00         | 1.00          | 0.47         | 0.50         | 0.58         | 0.57          |
| $m_0(t) = (-0.5t + 0.5)_+, \beta = (0.5, -0.5)^T$ |              |               |              |
| BIAS             | -0.002       | 0.010         | -0.011       | 0.015        | -0.006       | 0.012         |
| SD               | 0.069        | 0.126         | 0.107        | 0.196        | 0.093        | 0.174         |
| SE               | 0.074        | 0.128         | 0.110        | 0.190        | 0.099        | 0.172         |
| CP               | 96.2         | 94.8          | 93.8         | 93.0         | 95.2         | 94.0          |
| RE               | 1.00         | 1.00          | 0.41         | 0.41         | 0.55         | 0.52          |
| $m_0(t) = (-0.5t + 1)_+, \beta = (0, 0)^T$ |              |               |              |
| BIAS             | 0.002        | -0.005        | -0.002       | 0.001        | 0.002        | -0.007        |
| SD               | 0.069        | 0.115         | 0.111        | 0.179        | 0.094        | 0.158         |
| SE               | 0.073        | 0.127         | 0.106        | 0.183        | 0.096        | 0.166         |
| CP               | 96.4         | 97.4          | 92.0         | 92.8         | 93.8         | 95.8          |
| RE               | 1.00         | 1.00          | 0.38         | 0.41         | 0.54         | 0.53          |
| $m_0(t) = (-0.5t + 1)_+, \beta = (0, 0)^T$ |              |               |              |
| BIAS             | -0.001       | -0.010        | -0.004       | -0.013       | -0.003       | -0.003        |
| SD               | 0.056        | 0.096         | 0.085        | 0.147        | 0.072        | 0.123         |
| SE               | 0.059        | 0.102         | 0.082        | 0.142        | 0.075        | 0.129         |
| CP               | 96.8         | 96.0          | 94.0         | 93.0         | 94.4         | 95.6          |
| RE               | 1.00         | 1.00          | 0.43         | 0.43         | 0.58         | 0.59          |
| $m_0(t) = (-0.5t + 1)_+, \beta = (0.5, -0.5)^T$ |              |               |              |
| BIAS             | -0.003       | 0.001         | -0.003       | 0.004        | -0.009       | 0.002         |
| SD               | 0.075        | 0.133         | 0.110        | 0.195        | 0.095        | 0.181         |
| SE               | 0.074        | 0.129         | 0.111        | 0.191        | 0.099        | 0.172         |
| CP               | 94.8         | 93.8          | 92.6         | 91.0         | 94.4         | 92.8          |
| RE               | 1.00         | 1.00          | 0.46         | 0.47         | 0.64         | 0.54          |

BIAS, the empirical bias; SD, the empirical standard deviation; SE, the mean of estimated standard error; CP, the empirical coverage probability of 95% confidence interval; RE, the empirical relative efficiencies, calculated by the ratio of sample variance with the full estimators as a reference.
tervals have reasonable coverage rates. Compared to the full cohort analysis, the case-cohort designs are less efficient in estimating the regression coefficients but the efficiency loss appears to be small. We also find that the empirical relative efficiencies increase when the size of the subcohort increases.

Table 3: Comparison of weighted and unweighted estimators with $p_z = 0.5$

|               | Unweighted          | Weighted            |
|---------------|---------------------|---------------------|
|               | Full Subcohort:300  | Full Subcohort:300  |
| $m_0(t) = 1, \beta_0 = 0$ |                     |                     |
| BIAS          | -0.001 -0.003       | -0.001 -0.003       |
| SD            | 0.095 0.111         | 0.095 0.110         |
| SE            | 0.097 0.114         | 0.096 0.113         |
| CP            | 96.8 96.8           | 96.0 96.4           |
| $m_0(t) = 1, \beta_0 = 0.2$ |                     |                     |
| BIAS          | 0.003 -0.008        | 0.002 -0.008        |
| SD            | 0.100 0.120         | 0.100 0.119         |
| SE            | 0.100 0.118         | 0.101 0.118         |
| CP            | 94.2 95.0           | 94.4 95.0           |
| $m_0(t) = 1, \beta_0 = 0.5$ |                     |                     |
| BIAS          | 0.012 0.005         | 0.010 0.003         |
| SD            | 0.111 0.125         | 0.111 0.125         |
| SE            | 0.108 0.128         | 0.101 0.125         |
| CP            | 94.0 94.8           | 92.8 94.8           |
| $m_0(t) = 1 + t, \beta_0 = 0$ |                     |                     |
| BIAS          | 0.011 0.011         | 0.010 0.010         |
| SD            | 0.176 0.206         | 0.176 0.205         |
| SE            | 0.170 0.201         | 0.162 0.191         |
| CP            | 94.8 94.8           | 92.4 93.6           |
| $m_0(t) = 1 + t, \beta_0 = 0.2$ |                     |                     |
| BIAS          | -0.029 -0.032       | -0.029 -0.032       |
| SD            | 0.173 0.202         | 0.171 0.198         |
| SE            | 0.170 0.201         | 0.155 0.191         |
| CP            | 93.8 94.4           | 92.0 93.4           |
| $m_0(t) = 1 + t, \beta_0 = 0.5$ |                     |                     |
| BIAS          | -0.072 -0.073       | -0.072 -0.073       |
| SD            | 0.171 0.203         | 0.172 0.202         |
| SE            | 0.170 0.203         | 0.161 0.197         |
| CP            | 93.0 92.6           | 92.2 94.0           |

BIAS, the empirical bias; SD, the empirical standard deviation; SE, the mean of estimated standard error; CP, the empirical coverage probability of 95% confidence interval.
Table 4: Comparison of classical and stratified case-cohort design

|          | \( p_z = 0.5 \) |          | \( p_z = 0.3 \) |
|----------|-----------------|----------|-----------------|
|          | \( m_0(t) = 1, \ \beta_0 = 0 \) |          | \( m_0(t) = 1, \ \beta_0 = 0.2 \) |          | \( m_0(t) = 1 + t, \ \beta_0 = 0 \) |          | \( m_0(t) = 1 + t, \ \beta_0 = 0.2 \) |          | \( m_0(t) = 1 + t, \ \beta_0 = 0.5 \) |
|          | Full  | SRS   | STRAT  | Full  | SRS   | STRAT  | Full  | SRS   | STRAT  | Full  | SRS   | STRAT  |
| BIAS     | 0.001 | 0.004 | -0.001 | -0.009 | -0.011 | -0.015 | 0.002 | -0.002 | -0.003 | 0.013 | 0.010 | -0.001 |
| SD       | 0.094 | 0.110 | 0.094  | 0.103  | 0.125  | 0.127  | 0.099 | 0.113  | 0.122  | 0.114 | 0.125  | 0.130  |
| SE       | 0.098 | 0.115 | 0.098  | 0.107  | 0.125  | 0.123  | 0.100 | 0.118  | 0.117  | 0.118 | 0.137  | 0.134  |
| CP       | 96.0  | 96.4  | 96.0   | 95.2   | 95.4   | 94.4   | 95.0  | 96.0   | 94.8   | 96.0  | 96.6   | 95.4   |
| BIAS     | 0.003 | -0.005 | -0.007 | 0.051  | 0.034  | 0.031  | 0.005 | 0.016  | 0.013  | -0.006 | -0.006 | -0.017 |
| SD       | 0.110 | 0.123  | 0.132  | 0.142  | 0.142  | 0.151  | 0.110 | 0.128  | 0.128  | 0.141 | 0.162  | 0.161  |
| SE       | 0.107 | 0.128  | 0.128  | 0.141  | 0.162  | 0.161  | 0.107 | 0.128  | 0.128  | 0.141 | 0.162  | 0.161  |
| CP       | 94.8  | 94.4  | 93.8   | 96.0   | 96.2   | 96.4   | 94.8  | 94.0   | 92.4   | 96.0  | 96.2   | 95.4   |
| BIAS     | 0.005 | 0.016  | 0.013  | -0.006 | -0.006 | -0.017 | -0.021 | -0.025 | -0.030 | -0.014 | -0.014 | -0.022 |
| SD       | 0.173 | 0.208  | 0.206  | 0.191  | 0.225  | 0.229  | 0.170 | 0.200  | 0.202  | 0.184 | 0.218  | 0.213  |
| SE       | 0.170 | 0.200  | 0.201  | 0.184  | 0.218  | 0.213  | 0.169 | 0.200  | 0.201  | 0.199 | 0.235  | 0.229  |
| CP       | 93.6  | 93.0  | 93.4   | 94.2   | 95.0   | 92.8   | 94.0  | 94.6   | 92.4   | 96.0  | 96.2   | 95.4   |
| BIAS     | -0.021 | -0.025 | -0.030 | -0.014 | -0.014 | -0.022 | -0.070 | -0.081 | -0.078 | -0.027 | -0.046 | -0.053 |
| SD       | 0.170 | 0.206  | 0.209  | 0.192  | 0.222  | 0.218  | 0.181 | 0.199  | 0.214  | 0.212 | 0.253  | 0.241  |
| SE       | 0.170 | 0.202  | 0.210  | 0.218  | 0.255  | 0.252  | 0.178 | 0.202  | 0.210  | 0.218 | 0.255  | 0.252  |
| CP       | 92.4  | 93.2  | 93.6   | 94.8   | 93.4   | 93.4   | 92.4  | 93.2   | 93.6   | 94.8  | 93.4   | 93.4   |

SRS, the simple random sampling; STRAT, stratified case-cohort design with \( \eta = \nu = 0.7 \).
In the second scenario of simulation studies, we explore two improving approaches for the efficiency. One method is to use the weighted function \( m(t|Z) = m_0(t) \exp(\beta_0 Z) \), the other method is to use the stratified case-cohort design. Here the event time \( T \) is generated from

\[
m(t|Z) = m_0(t) \exp(\beta_0 Z),
\]

where the covariate \( Z = 2 \times \text{Bernoulli}(p_z) - 1 \) with \( p_z = 0.3 \) or 0.5, the true regression parameter \( \beta_0 \) is set to be 0, 0.2 or 0.5, the baseline function \( m_0(t) \) is taken from \( m_0(t) = 1 \) or \( m_0(t) = 1 + t \), respectively. \( C \) is generated as described in the first scenario of simulations, but the censoring rates are set approximately 90% this time. The sample size and the subcohort size are almost equal to the first ones. The simulation results using the weighted estimating equations can be found in Table 3, where we can conclude that the weighted estimators tend to be much more efficient than the unweighted ones, especially for the case-cohort study. But the weighted case-cohort estimators are still not efficient as the full estimators, this is in accordance with our expectation since we only use the uncensored data and the subcohort data under the case-cohort design.

In the stratified case-cohort design simulation, we define the distribution of \( Z^* \) by \( \eta = \text{Pr}(Z^* = 1|Z = 1) \) and \( \nu = \text{Pr}(Z^* = -1|Z = -1) \), where \( (\eta, \nu) \) is chosen as \((0.7, 0.7)\). Thus \( Z^* = 2 \times \text{Bernoulli}((1 - \nu)(1 - p_z) + \eta \cdot p_z) - 1 \). The subcohort is a stratified sample selected by independent Bernoulli sampling with selection probability \( p(Z^*) \) chosen so that approximately equal numbers of subjects are selected from the two strata, \( \{Z^* = 1\} \) and \( \{Z^* = -1\} \). Simulation results comparing the full, classical, stratified cohort are given in Table 4. In general, the stratified case-cohort design behaves better than the classical one when the correlation between \( Z \) and \( Z^* \) exists. But when \( Z \) and \( Z^* \) are uncorrelated, the classical case-cohort design will do slightly better than the stratified one.

4 A Real Data Example

In this Section, we apply the proposed case-cohort analysis approach under the proportional mean residual life model to the South Welsh nickel refiners study. In this study, men employed in a nickel refinery in South Wales were investigated to determine the risk of developing carcinoma of the bronchi and nasal sinuses which is associated with the refining of nickel. The cohort was identified using the weekly payrolls of the company and followed from the year 1934 until 1981. The complete records of 679 workers employed before 1925 can be obtained from the Appendix VIII in [Breslow and Day (1987)](#). Among the full cohort, there
were 56 deaths from cancer of the nasal sinus until 1981. The event rate for this study is quite low and hence the case-cohort design is more likely to be applied. Breslow and Day (1987) used the Cox model to analyse the mortality data on nasal sinus cancer. They considered the survival time to be years since first employment and found three significant risk factors: AFE (age at first employment), YFE (year at first employment) and EXP (exposure level). Lin and Ying (1993) fitted the same model to the data obtained from a “hypothetical” case-cohort design which was randomly selected 100 subcohort members from the entire cohort. In this paper, we fit respectively the mean residual life model to the full cohort and the case-cohort in which a subcohort with size 100 is drawn by simple random sampling. The covariates transformations adopted by Breslow and Day (1987) are reserved here. Specifically, we consider four covariates: log(AFE-10), (YFE-1915)/10, (YFE-1915)^2/100 and log(EXP+1). In Table 5, we present estimates and standard errors of the regression coefficients under proportional mean residual life model for the two cases.

Table 5: Regression Analyses of Time from the First Employment to the Nasal Sinus Cancer Death for the Welsh Nickel Refines Study

| Parameter                  | Unweighted | Weighted |
|----------------------------|------------|----------|
|                            | Full Cohort | Case-cohort | Full Cohort | Case-cohort |
| log (AFE-10)               |            |           |            |            |
| Est.                       | -0.096     | -0.060    | -0.097     | -0.062     |
| S.E.                       | 0.007      | 0.014     | 0.006      | 0.012      |
| P Value                    | <0.0001    | <0.0001   | <0.0001    | <0.0001    |
| (YFE-1915)/10              |            |           |            |            |
| Est.                       | -0.009     | -0.024    | -0.010     | -0.025     |
| S.E.                       | 0.013      | 0.019     | 0.013      | 0.018      |
| P Value                    | 0.475      | 0.195     | 0.442      | 0.184      |
| (YFE-1915)^2/10            |            |           |            |            |
| Est.                       | 0.090      | 0.064     | 0.091      | 0.066      |
| S.E.                       | 0.026      | 0.035     | 0.025      | 0.034      |
| P Value                    | 0.0005     | 0.066     | 0.001      | 0.052      |
| log(EXP+1)                 |            |           |            |            |
| Est.                       | -0.057     | -0.057    | -0.057     | -0.059     |
| S.E.                       | 0.013      | 0.016     | 0.012      | 0.016      |
| P Value                    | <0.0001    | 0.0005    | <0.0001    | 0.0002     |

Est., Parameter Estimate; S.E., Standard Error.

In general, the case-cohort estimates for each covariate are close to the corresponding full-cohort estimates. This implies that the case-cohort analysis results are convincing. Both
the full cohort and case-cohort analysis results under proportional mean residual life model indicate that the covariates \( \log(AFE-10) \), \( (YFE-1915)^2 / 100 \) and \( \log(EXP+1) \) have significant influence on the survival time, which in accordance with the results indicate by the Cox model under full cohort. The results of the estimated coefficients show two different scenes: the mean residual life decreases with the individual’s AFE or EXP increasing, but has performance for \( (YFE-1915)^2 / 100 \) on the contrary. It is interesting that the regression coefficients for those significant covariates based on the proportional mean residual life model have opposite signs to their counterparts under the Cox model. This phenomenon also appeared in the real data analysis of Chen and Cheng (2005) because of the different link between the proportional mean residual life model and the Cox model.

5 Concluding Remarks

In this paper, we proposed some new estimating functions to deal with case-cohort data under proportional mean residual life model. Appropriate weighted availability indicators are defined when the subcohort is drawn by simple random sampling. The large sample properties of the proposed estimators are established.

A practical problem is how to improve the estimate efficiency. For case-cohort analysis under the Cox model, Kulich and Lin (2004) suggested estimating the sampling probability \( p \) with a weight estimator to achieve further efficiency. Inspired by the idea, we can consider the weighted estimator proposed in Chen and Zucker (2009) for \( p \) by

\[
\hat{p}(t) = \frac{\sum_{i=1}^{n} \xi_i (1 - \delta_i) c_i(t)}{\sum_{i=1}^{n} (1 - \delta_i) c_i(t)},
\]

where \( c_i(t) \) is possibly time-dependent and satisfy some regularity conditions. Under the Cox model, various versions of the weight \( c_i(t) \) for estimating the sampling probability \( p \), including both time-constant and time-dependent weights, has been suggested by Chen and Lo (1999), Borgan et al. (2000) and Kulich and Lin (2004). Two common choices for \( c_i(t) \) are \( c_i(t) = 1 \) and \( c_i(t) = Y_i(t) \), where \( Y_i(t) \) is defined in section 2. Similarly, in mean residual life model, a Horvitz-Thompson weighted function \( \pi_i(t) = \delta_i + (1 - \delta_i) \xi_i / \hat{p}(t) \) can be considered to replace \( \pi_i \) in the estimating equations (5) and (8).

6 Appendix

Proof of the Theorem

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(i) Note that
\[
\hat{m}_0(t; \beta) = \frac{1}{S_n(t)} \int_t^\tau S_n(u) \sum_{i=1}^n \pi_i Y_i(u) \exp(-\beta^\top Z_i) du \\
= \frac{1}{E[S(t|Z)]} \int_t^\tau E[S(u|Z)] \frac{\int_z S(u|z) \exp(-\beta^\top z) dF_z(z)}{E[S(u|Z)]} du + o_p(1) \\
= \frac{E[\exp(-\beta^\top Z) \int_t^\tau S(u|Z) du]}{E[S(t|Z)]} + o_p(1) \\
\triangleq m_0(t; \beta) + o_p(1),
\]
where \( F_z(z) \) is the distribution function of \( Z \) and \( S(t|Z) \) is the survival function of \( T \) given \( Z \). This implies that \( \hat{m}_0(t; \beta) \) converges in probability to \( m_0(t; \beta) \) uniformly in \( t \in [0, \tau] \) and \( \beta \) in a compact set which contains the true parameter \( \beta_* \), and \( m_0(t; \beta_*) = m_*(t) \). Therefore, to prove the existence of \( \hat{\beta} \) and \( \hat{m}_0(t) \), it suffices to show that there exists a solution to \( U(\beta) = 0 \). By differentiating \( U(\beta) \) with respect to \( \beta \), we have
\[
\hat{A}(\beta_*) \triangleq \frac{\partial U(\beta)}{\partial \beta} \bigg|_{\beta = \beta_*} \\
= \frac{1}{n} \sum_{i=1}^n \int_0^\tau \pi_i \{ Z_i - \bar{Z}(t) \} \left\{ -m_*(t) \mu_*(t) dN_i(t) + Z_i \exp(-\beta_*^\top Z_i) Y_i(t) dt \right\}^\top + o_p(1) \\
= \frac{1}{n} \sum_{i=1}^n \int_0^\tau \pi_i \{ Z_i - \bar{Z}(t) \} \left\{ -m_*(t) \mu_*(t) \right\}^\top dM_i(t) \\
+ \frac{1}{n} \sum_{i=1}^n \int_0^\tau \pi_i \{ Z_i - \bar{Z}(t) \} \left\{ Z_i - \mu_*(t) \right\}^\top \exp(-\beta_*^\top Z_i) Y_i(t) dt + o_p(1) \\
= A + o_p(1),
\]
this implies that \( \hat{A}(\beta_*) \) converges in probability to a nonrandom \( A \). Since \( U(\beta_*) \to 0 \) almost surely, and \( A \) is nonsingular by the regularity condition C4, the convergence of \( \hat{A}(\beta_*) \) implies that we can find a small neighborhood of \( \beta_* \) in which \( \hat{A}(\beta_*) \) is nonsingular when \( n \) is large enough. Hence it follows from the inverse function theorem that within a small neighborhood of \( \beta_* \), there exists a solution \( \hat{\beta} \) to \( U(\hat{\beta}) = 0 \) for sufficiently large \( n \). Notice that \( \hat{\beta} \) is strongly consistent to \( \beta_* \), then it follows from the uniform convergence of \( \hat{m}_0(t; \beta) \) to \( m_0(t; \beta) \) that \( \hat{m}_0(t) \triangleq \hat{m}_0(t; \hat{\beta}) \to m_0(t; \beta_*) = m_*(t) \) almost surely in \([0, \tau] \).
(ii) Write \( U(\beta_*) \triangleq U(\beta_*, \hat{m}_0(t; \beta_*)) \), since

\[
U(\beta_*, m_*(\cdot)) = \frac{1}{n} \sum_{i=1}^{n} \int_{0}^{r} \pi_i Z_i [m_*(t) dN_i(t) - Y_i(t) \{\exp(-\beta_*^T Z_i) dt + dm_*(t)\}],
\]

and

\[
U(\beta_*, \hat{m}_0(t; \beta_*)) - U(\beta_*, m_*(\cdot))
\]

\[
= \frac{1}{n} \sum_{i=1}^{n} \int_{0}^{r} \pi_i Z_i \left[ \{\hat{m}_0(t; \beta_*) - m_*(t)\} dN_i(t) - Y_i(t) \left\{\frac{\sum_{i=1}^{n} \pi_i dN_i(t)}{\sum_{i=1}^{n} \pi_i Y_i(t)} \right\} \right]
\]

\[
= \frac{1}{n} \sum_{i=1}^{n} \int_{0}^{r} \pi_i [Z_i - \bar{Z}(t)] dN_i(t) \{\hat{m}_0(t; \beta_*) - m_*(t)\} - \frac{1}{n} \sum_{i=1}^{n} \int_{0}^{r} \pi_i \bar{Z}(t) m_*(t) dM_i(t, \beta_*, m_*)
\]

\[
= \frac{1}{n} \sum_{i=1}^{n} \int_{0}^{r} \pi_i [Z_i - \bar{Z}(t)] dN_i(t) \left\{-\frac{1}{S_n(t)} \int_{t}^{r} \frac{S_n(u)}{C_n(u)} \frac{1}{n} \sum_{i=1}^{n} \pi_i m_*(u) dM_i(u; \beta_*, m_*)\right\}
\]

\[-\frac{1}{n} \sum_{i=1}^{n} \int_{0}^{r} \pi_i \bar{Z}(t) m_*(t) dM_i(t, \beta_*, m_*)
\]

\[
= \frac{1}{n} \sum_{i=1}^{n} \int_{0}^{r} \pi_i \bar{Z}(t) [m_*(t) dM_i(t, \beta_*, m_*)]
\]

therefore

\[
n^{1/2} U(\beta_*) = n^{1/2} U(\beta_*, \hat{m}_0(t; \beta_*))
\]

\[
= n^{1/2} U(\beta_*, m_*(\cdot)) + n^{1/2} U(\beta_*, \hat{m}_0(t; \beta_*)) - U(\beta_*, m_*(\cdot))
\]

\[
= \frac{1}{n} \sum_{i=1}^{n} \int_{0}^{r} \pi_i \left[ Z_i - \bar{Z}(t) - \bar{Z}(t) \right] m_*(t) dM_i(t, \beta_*, m_*)
\]

\[
= \frac{1}{n} \sum_{i=1}^{n} \int_{0}^{r} \pi_i \left[ Z_i - \mu_Z(t) - \bar{\mu}_Z(t) \right] m_*(t) dM_i(t, \beta_*, m_*) + o_p(1)
\]

\[
= \frac{1}{n} \sum_{i=1}^{n} \int_{0}^{r} \left( \pi_i - 1 \right) [Z_i - \mu_Z(t) - \bar{\mu}_Z(t)] m_*(t) dM_i(t, \beta_*, m_*) + o_p(1)
\]
\[ \sum_{i=1}^{n} \int_{0}^{\tau} [Z_i - \mu_{z}(t) - \tilde{\mu}_{z}(t)] m_{s}(t) dM_{i}(t, \beta_{s}, m_{s}) \]

\[ -n^{-1/2} \sum_{i=1}^{n} \int_{0}^{\tau} (1 - \delta_{i})(1 - \xi_{i}/p) [Z_i - \mu_{z}(t) - \tilde{\mu}_{z}(t)] m_{s}(t) dM_{i}(t, \beta_{s}, m_{s}) + o_p(1). \]

Let \( \mathcal{F}_i \) be the \( \sigma \)-field generated by \( \{ \bar{T}_i, \delta_i, Z_i \} \), and

\[ \eta_i = (1 - \delta_{i}) \int_{0}^{\tau} [Z_i - \mu_{z}(t) - \tilde{\mu}_{z}(t)] m_{s}(t) dM_{i}(t, \beta_{s}, m_{s}). \]

It is easy to see that \( E(1 - \xi_{i}/p|\mathcal{F}_i) = 0 \), \( E\{\eta_{i}(1 - \xi_{i}/p)|\mathcal{F}_i\} = E\{\eta_{i}E(1 - \xi_{i}/p|\mathcal{F}_i)\} = 0 \) and \( \text{var}\{\eta_{i}(1 - \xi_{i}/p)\} = E\{\eta_{i}^{2}\text{var}(1 - \xi_{i}/p|\mathcal{F}_i)\} - E\{\eta_{i}\text{var}(1 - \xi_{i}/p|\mathcal{F}_i)\}^{2} = (1 - p)/p\{E[\eta_{i}^{2} - E[\eta_{i}^{2}]} \} = \Sigma_{2}. \) Also, conditional on \( \mathcal{F}_i \), \( \{\eta_{i}(1 - \xi_{i}/p), i = 1, \ldots, n\} \) and the first term of \( n^{1/2}U(\beta_{s}) \) are uncorrelated, and hence \( n^{1/2}U(\beta_{s}) \) is asymptotically normal with mean zero and variance-covariance matrix \( \Sigma = \Sigma_{1} + \Sigma_{2} \). Thus, the Taylor expansion of \( U(\beta) \) at \( \beta_{s} \) gives

\[ n^{1/2}(\hat{\beta} - \beta_{s}) = -A^{-1}n^{1/2}U(\beta_{s}) + o_p(1) \]

\[ = -A^{-1}n^{-1/2} \sum_{i=1}^{n} \int_{0}^{\tau} \pi_i [Z_i - \mu_{z}(t) - \tilde{\mu}_{z}(t)] m_{s}(t) dM_{i}(t, \beta_{s}, m_{s}) + o_p(1). \]

(iii) Let \( \zeta_i = \int_{0}^{\tau} [Z_i - \mu_{z}(t) - \tilde{\mu}_{z}(t)] m_{s}(t) dM_{i}(t, \beta_{s}, m_{s}). \) Write

\[ n^{1/2}\{\hat{m}_{0}(t) - m_{s}(t)\} \]

\[ = n^{1/2}\{\hat{m}_{0}(t; \hat{\beta}) - \hat{m}_{0}(t; \beta_{s})\} + n^{1/2}\{\hat{m}_{0}(t; \beta_{s}) - m_{s}(t)\} \]

\[ = \left( \frac{\partial \hat{m}_{0}(t; \beta)}{\partial \beta} \right|_{\beta = \beta_{s}} \right)^{\top} n^{1/2}(\hat{\beta} - \beta_{s}) + n^{1/2}\{\hat{m}_{0}(t; \beta_{s}) - m_{s}(t)\} + o_p(1). \]

Now, we establish the formula of \( \hat{m}_{0}(t; \beta_{s}) - m_{s}(t) \). By inserting \( \{\beta_{s}, m_{s}(t)\} \) and \( \{\beta_{s}, \hat{m}_{0}(t; \beta_{s})\} \) into (5), respectively, we have

\[ \sum_{i=1}^{n} \pi_i \left[ m_{s}(t) dN_i(t) - Y_i(t) \{ \exp(-\beta_{s}^{\top} Z_i) dt + dm_{s}(t) \} \right] = \sum_{i=1}^{n} \pi_i m_{s}(t) dM_{i}(t, \beta_{s}, m_{s}), \quad (14) \]

\[ \sum_{i=1}^{n} \pi_i \left[ \hat{m}_{0}(t; \beta_{s}) dN_i(t) - Y_i(t) \{ \exp(-\beta_{s}^{\top} Z_i) dt + d\hat{m}_{0}(t; \beta_{s}) \} \right] = 0. \quad (15) \]

Subtracting (14) from (15),

\[ \sum_{i=1}^{n} \pi_i \left[ \{\hat{m}_{0}(t; \beta_{s}) - m_{s}(t)\} dN_i(t) - Y_i(t) d \{\hat{m}_{0}(t; \beta_{s}) - m_{s}(t)\} \right] = - \sum_{i=1}^{n} \pi_i m_{s}(t) dM_{i}(t, \beta_{s}, m_{s}), \]
which is equivalent to
\[
\sum_{i=1}^{n} \frac{\pi_i dN_i(t)}{\sum_{i=1}^{n} \pi_i Y_i(t)} \{ \hat{m}_0(t; \beta) - m_*(t) \} - d \{ \hat{m}_0(t; \beta) - m_*(t) \} = -\sum_{i=1}^{n} \pi_i m_*(t) dM_i(t; \beta_*, m_*) / \sum_{i=1}^{n} \pi_i Y_i(t).
\]
Then
\[
\hat{m}_0(t; \beta) - m_*(t) = -\frac{1}{S_n(t)} \int_t^\tau \frac{S_n(u)}{C_n(u)} n \sum_{i=1}^{n} \pi_i m_*(u) dM_i(u; \beta_*, m_*) + O_p(1)
\]
Hence
\[
n^{1/2} \{ \hat{m}_0(t) - m_*(t) \} = m_*(t) \mu_z(t) A^{-1} n^{-1/2} \sum_{i=1}^{n} \pi_i \xi_i - \frac{1}{S_n(t)} \int_t^\tau \frac{S_n(u)}{C_n(u)} n^{-1/2} \sum_{i=1}^{n} \pi_i m_*(u) dM_i(u; \beta_*, m_*) + O_p(1)
\]
\[
= m_*(t) \mu_z(t) A^{-1} n^{-1/2} \sum_{i=1}^{n} \pi_i \xi_i - \frac{1}{S(t)} \int_t^\tau \frac{S(u)}{C(u)} n^{-1/2} \sum_{i=1}^{n} \pi_i m_*(u) dM_i(u; \beta_*, m_*) + O_p(1)
\]
\[
= n^{-1/2} \sum_{i=1}^{n} \pi_i \left[ m_*(t) \mu_z(t) A^{-1} \xi_i - \frac{1}{S(t)} \int_t^\tau \frac{S(u)}{C(u)} m_*(u) dM_i(u; \beta_*, m_*) \right] + O_p(1)
\]
\[
= n^{-1/2} \sum_{i=1}^{n} \varphi_i(t) - n^{-1/2} \sum_{i=1}^{n} (1 - \delta_i)(1 - \xi_i/p) \varphi_i(t) + O_p(1),
\]
where
\[
\varphi_i(t) = m_*(t) \mu_z(t) A^{-1} \xi_i - \frac{1}{S(t)} \int_t^\tau \frac{S(u)}{C(u)} m_*(u) dM_i(u; \beta_*, m_*),
\]
\(S(t)\) and \(C(t)\) are the uniform limit of \(S_n(t)\) and \(C_n(t)\) respectively. Because \(\varphi_i(\cdot)(i = 1, \ldots, n)\) are independent mean zero random variables for each \(t\), by Pollard (1990), \(n^{1/2} \{ \hat{m}_0(t) - m_*(t) \} \{0 \leq t \leq \tau\} \) converges weakly to a mean zero Gaussian process, whose covariance function at \((s, t)\) is
\[
E[\varphi_1(s) \varphi_1(t)] + \frac{1-p}{p} E[(1-\delta) \varphi_1(s) \varphi_1(t)] - \frac{1-p}{p} E[(1-\delta) \varphi_1(s)] E[(1-\delta) \varphi_1(t)].
\]

**Acknowledgements**

The authors wish to express their appreciation to Professor Yingqing Chen and Cindy Zhang for their invaluable assistance of the original version. Ma’s work is partially supported by National Institutes of Health grant R01 HL113548. Shi’s work was supported by Natural Science Foundation of Fujian Province, China (2016J01026). Zhou’s work was partially supported by National Natural Science Foundation of China (NSFC) (71271128), the State
Key Program of National Natural Science Foundation of China (71331006), Science Fund for Creative Research Groups (11021161), NCMIS, Shanghai Leading Academic Discipline Project A and IRTSHUFE.

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