SEMIPARAMETRIC TIME-VARYING COEFFICIENT REGRESSION MODEL FOR LONGITUDINAL DATA WITH CENSORED TIME ORIGIN

by

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ABSTRACT

QIONG SHOU. Semiparametric time-varying coefficient regression model for longitudinal data with censored time origin. (Under the direction of DR. YANQING SUN)

In preventive HIV vaccine efficacy trials, thousands of HIV-negative volunteers are randomized to receive vaccine or placebo, and are monitored for HIV infection. The primary objective is to assess vaccine efficacy to prevent HIV infection. An important aspect of vaccine efficacy trials is to assess whether vaccine decreases secondary transmission of HIV and ameliorates HIV disease progression in vaccine recipients who become infected.

This dissertation investigates the vaccine effect on the post HIV longitudinal biomarkers (e.g., viral loads and CD4 counts) over time since the actual HIV acquisition. The method applies to the situation when the time of the actual HIV acquisition may be missing or censored.

The problem is investigated under the semiparametric additive time-varying coefficient model where the influences of some covariates vary nonparametrically with time while the effects of the other covariates remain constant. The weighted profile least squares estimators are developed for the unknown parameters as well as for the nonparametric coefficient functions. The method uses the expectation maximization approach to deal with the censored time origin. The asymptotic properties of both the parametric and nonparametric estimators are derived and the consistent estimates of the asymptotic variances are given. The numerical simulations are conducted to examine finite sample properties of the proposed estimators. The method is also applied to a real data from the STEP study with MITT cases.

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CHAPTER 1: INTRODUCTION

1.1 A motivating example

In preventive HIV vaccine efficacy trials, thousands of HIV-negative volunteers are randomized to receive vaccine or placebo, and are monitored for HIV infection. The primary objective is to assess vaccine efficacy to prevent HIV infection. An important aspect of vaccine efficacy trials is to assess whether vaccine decreases secondary transmission of HIV and ameliorates HIV disease progression in vaccine recipients who become infected (cf., Clemens *et al.*, 1997; Halloran *et al.*, 1997; Clements-Mann, 1998; Nabel, 2001; Shiver *et al.*, 2002; HVTN, 2004; IAVI, 2004).

We propose to investigate the vaccine effect on the post HIV longitudinal biomarkers (e.g., viral loads and CD4 counts). Viral load and CD4 counts have been found to be highly prognostic for both secondary transmission and progression to clinical disease in observational studies (cf., Mellors *et al.*, 1997; HIV Surrogate Marker Collaborative Group, 2000; Quinn *et al.*, 2000; Gray *et al.*, 2001). All previous analyses of HIV vaccine efficacy trials assessed these biomarkers based on the time from HIV positive diagnosis. However, it is biologically meaningful to assess whether vaccination modifies or accelerates the development of these biomarkers over time since the actual HIV acquisition. This assessment can be challenging since exact times of actual HIV acquisition are often unobtainable for trial participants. A brief description of HIV vaccine efficacy trial's diagnosis algorithm is given in the following.

HIV vaccine trials test volunteers for anti-HIV antibodies at periodic intervals (e.g., every 3 or 6 months); these antibody-based tests have near-perfect sensitivity to detect infections that occurred at least four weeks ago but otherwise may miss the infection. For all subjects with an HIV antibody positive (Ab+) test, a "look-back" procedure is applied wherein earlier available blood samples are tested for HIV infection using a more sensitive antigen-based HIV-specific PCR assay, which has near-perfect sensitivity if the infection occurred at least one week ago. Therefore, each infected subject is classified into one of two groups, defined by whether the *earliest* HIV positive sample is Ab- and PCR+ or is Ab+ and PCR+. The actual HIV acquisition time is approximated well by the time at Ab- and PCR+, while actual infection time occur approximately between the first Ab+ and earlier Ab- test times in the case of Ab+ and PCR+. The Ab+ and PCR+ cases occur in between 20% and 70% of infected subjects, with the rate depending on the frequency of HIV testing.

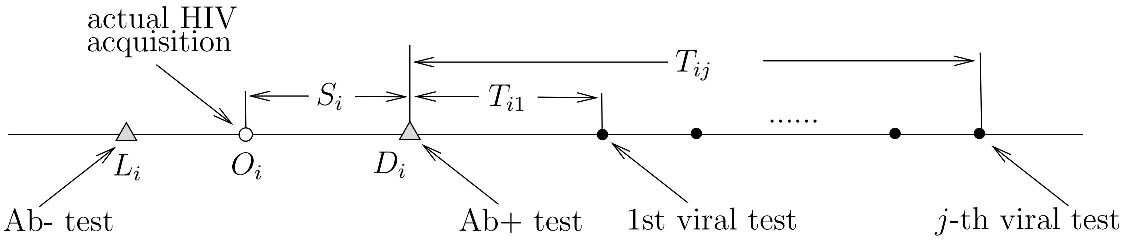


Figure 1.1: Time since actual HIV acqusition in case of Ab+ and PCR+.

Consider the ith subject, $i = 1, \ldots, n$, who becomes HIV infected during the HIV vaccine efficacy trial. Let O_i be the time of actual HIV acquisition, D_i the HIV positive diagnosis time based on the trial's diagnosis algorithm (first Ab+ test time) and L_i the last Ab- test time. Post-infection biomarkers are measured at times $T_{i1}, \ldots, T_{in_i}$, where T_{ij} is the time between the first Ab+ and the time at which the jth measurement is taken. Let S_i be the gap between HIV acquisition and the diagnosis, $S_i = D_i - O_i$. If subject i has an acute sample (Ab- and PCR+), the actual infection time can be well approximated by L_i and in this case let $S_i = D_i - L_i$. Otherwise, S_i is less than $D_i - L_i$. The S_i (time origin) is left censored by $D_i - L_i$ with censoring indicator R_i: $R_i = 1$ if S_i is observed and $R_i = 0$ if S_i is less than $D_i - L_i$. The time from actual HIV acquisition to the jth sampling time is then $T_{ij}^o = S_i + T_{ij}$. Figure 1.1 illustrates the set-up.

1.2 Existing works

The sampling times $T_{ij}^o = S_i + T_{ij}$ from the actual HIV acquisition are known when S_i is completely observed. In this case many existing statistical methods can be used to analyze model (2.1). Among others, recent works in this area include semiparametric methods by Moyeed & Diggle (1994), Zeger & Diggle (1994), and Liang, Wu & Carroll (2003), nonparametric methods by Hoover, Rice, Wu & Yang (1998), Wu, Chiang & Hoover (1998), Scheike & Zhang (1998), Wu & Zhang (2002), Wu & Liang (2004) and Sun & Wu (2003). Martinussen & Scheike (1999, 2000, 2001) and Lin & Ying (2001) considered time-varying coefficients regression models for longitudinal data and successfully integrated counting process techniques into the analysis of longitudinal data, providing further bridging between survival analysis, recurrent events, and time-dependent observations. Sun and Wu (2005) developed weighted least squares estimation procedure which avoids modeling of the sampling times is asymptotically more efficient than a single nearest neighbor smoothing which depends on estimation of the sampling model.

CHAPTER 2: SAMPLING ADJUSTED PROFILE LOCAL LINEAR ESTIMATION APPROACH THROUGH EM ALGORITHM

2.1 Preliminaries

Suppose that there is a random sample of n subjects. For subject i, let $Y_i(t)$ be the response process and let $X_i(t)$ and $Z_i(t)$ be the possibly time-dependent covariates of dimensions $(p+1)\times 1$ and $q\times 1$, respectively, where t is the time since actual HIV acquisition. The proposed general semiparametric time-varying coefficients regression model assumes that

$$Y_i(t) = \beta^T(t)X_i(t) + \gamma^T Z_i(t) + \epsilon_i(t), \qquad i = 1,\ldots,n \tag{2.1}$$

where $\beta(t)$ is an unspecified $(p+1)\times 1$ vector of smooth regression functions, γ is a $q\times 1$ dimensional vector of parameters, and $\epsilon_i(t)$ is a mean-zero process. The notation x^T represents transpose of a vector or matrix x. The first component of $X(t)$ is specified as 1 in general, giving to a model with a nonparametric baseline. The effect of $X(t)$ is modeled nonparametrically while the effect of $Z(t)$ follows a given parameter.

The observations of $Y_i(t)$ are taken at time points $T_{i1}^o < T_{i2}^o < \cdots < T_{in_i}^o$, where n_i is the total number of observations on the ith subject. The observation times T_{ij}^o can be decomposed in two parts $T_{ij}^o = S_i + T_{ij}$ as shown in Figure 1.1, where S_i is the time from actual HIV acquisition to the first positive diagnosis test and T_{ij} is the time from the first positive diagnosis test to the jth visit for the ith subject. The number of observations taken on the ith subject by time t is $N_i^o(t) = \sum_{j=1}^{n_i} I(T_{ij}^o \le t)$, where $I(\cdot)$ is the indicator function. Let C_i be the end of follow-up time or censoring time for the ith subject starting at HIV positive diagnosis (Ab+ test time). The censoring time C_i will be allowed to depend on the covariates $X_i(\cdot)$ and $Z_i(\cdot)$. The responses for the ith subject can only be observed at the time points before C_i. The censoring time since the actual time origin (HIV acquisition) is $S_i + C_i$.

Let the conditional mean rate of the observation times $\alpha_i(t)$ for subject i be defined as

$$E\{dN_i^o(t) \mid X_i(t), Z_i(t)\} = \alpha(t, U_i(t))\, dt \equiv \alpha_i(t)\, dt, \qquad i = 1, \ldots, n, \tag{2.2}$$

where $U_i(t)$, a $m \times 1$ vector, is the part of the covariates $(X_i(t), Z_i(t))$ that affects the potential sampling times. The function $\alpha(t, u)$ is an unspecified nonnegative smooth function.

The time S_i from actual HIV acquisition to HIV positive diagnosis may be left censored by the censoring time V_i. Let $R_i = I(S_i \geq V_i)$ be the censoring indicator. For the application concerned in this paper, the censoring time V_i (e.g. $D_i - L_i$) is assumed to be observed for all subjects. Let $\mathcal{D}_i = \{V_i, C_i, A_i, T_{ij}, X_i(T_{ij}^o), Z_i(T_{ij}^o), Y_i(T_{ij}^o), j = 1, \ldots, n_i\}$, where A_i is a collection of possible auxiliary variables that are not of interest in the modelling of $Y_i(t)$ but may be useful in predicting the distribution of S_i. The observed data for subject i can be expressed as $\mathcal{X}_i = \{R_i S_i, R_i, \mathcal{D}_i\}$. The observation is $\{S_i, \mathcal{D}_i\}$ if $R_i = 1$ and $\mathcal{D}_i$ if $R_i = 0$. Although exact times T_{ij}^o may be unobtainable, the values $X_{ij} = X_i(T_{ij}^o)$, $Z_{ij} = Z_i(T_{ij}^o)$ and $Y_{ij} = Y_i(T_{ij}^o)$ at T_{ij}^o are known. Denote the observed data by $\mathcal{X} = \{\mathcal{X}_i, i = 1, 2, \ldots, n\}$.

Assume that S_i and V_i are independent, and that the censoring time C_i is non-informative in the sense that $E\{dN_i^o(t) \,|X_i(t), Z_i(t), S_i + C_i \geq t\} = E\{dN_i^o(t)|X_i(t), Z_i(t)\}$ and $E\{Y_i(t)|X_i(t), Z_i(t), S_i + C_i \geq t\} = E\{Y_i(t)|X_i(t),\ Z_i(t)\}$. Let $N_i(t) = \sum_{j=1}^{n_i} I(T_{ij} \leq t)$. Assume $E\{Y_i(t)|X_i(\cdot), Z_i(\cdot), N_i(\cdot), S_i, V_i, C_i\} = E\{Y_i(t)|X_i(\cdot), Z_i(\cdot)\}$. Assume also that $Y_i(t)$ and $dN_i^o(t)$ are independent conditional on $X_i(t)$, $Z_i(t)$ and $S_i + C_i \geq t$. This assumption implies that, conditional on covariate processes, sampling times are noninformative for the response. Note that dependence between response and sampling times as well dependence between sampling times and the censoring time C_i is often induced by ignoring certain covariates (cf., Miloslavsky *et al.,* 2004 and Zeng, 2005). The stated conditional independence assumptions make the proposed methods applicable to situations where dependence may exist among response process, sampling times and censoring time C_i but becoming independent by including appropriate additional covariates. A recent work by Sun and Lee (2011) on testing independent censoring for longitudinal data provides needed procedures for checking such assumptions.

When all S_i's are observed, the existing statistical methods cited in Section 1.2 can be used to analyze model (2.1). However, none of these methods address the problem in which the time origin may be censored. We propose to extend the investigation of model (2.1) to accommodate this situation.

2.2 Estimation Procedures

It is important to note that if the unobserved or censored S_i is treated as missing, then S_i is not missing at random in the sense of Robin (1976). The inverse probability weighting of complete-cases method of Horvitz and Thompson (1952) and the augmented inverse probability weighted complete-case method of Robins, Rotnitzky and Zhao (1994), which have been successfully adapted in Sun and Gilbert (2011), Sun, Wang and Gilbert (2011) and by many other authors, will not work in this situation. We propose an estimation procedure based on the missing-data principle using the EM-algorithm. The EM-algorithm has been applied by Scheike and Sun (2007) to develop maximum likelihood estimation for tied survival data under Cox regression model.

Let $F_S(s|\mathcal{D}_i)$ be the conditional distribution of S_i given $\mathcal{D}_i$. The conditional distribution of S_i given $\mathcal{D}_i$ and $R_i = 0$, $F_S(s|\mathcal{D}_i, R_i = 0)$, equals $F_S(s|\mathcal{D}_i)/F_S(V_i|\mathcal{D}_i)$ for $s \leq V_i$ and 1 for $s > V_i$. Assume that $\max\{S_i, V_i\}$ is bounded by a predetermined constant c. This is reasonable since for the application concerned here $\max\{S_i, V_i\}$ is less than the time interval between two consecutive testing times which is usually between 3 and 6 months. The distribution of S_i based on the left censored data can be estimated by using the right censored data through the transformation $\{\min\{c - S_i, c - V_i\}, R_i = I(c - S_i \le c - V_i)\}$. Therefore, the Kaplan-Meier estimator can be used to estimate the distribution of S_i when S_i is independent of $\mathcal{D}_i$. Otherwise, a failure time regression model such as the Cox model (Cox, 1972) can be used to estimate the conditional distribution $F_S(s|\mathcal{D}_i)$. Observing the censoring time V_i for all subjects is a key factor in the estimation of $F_S(s|\mathcal{D}_i, R_i = 0)$. Otherwise $F_S(s|\mathcal{D}_i, R_i = 0)$ is not identifiable.

Let $\widehat{F}_S(s|\mathcal{D}_i)$ be the estimated conditional distribution of $F_S(s|\mathcal{D}_i)$. The probability $\pi_i = P(R_i = 1|\mathcal{D}_i) = P(S_i \ge V_i|\mathcal{D}_i)$ can be estimated by $\widehat{\pi}_i = 1 - \widehat{F}_S(V_i|\mathcal{D}_i)$. Let $dN_i^c(t) = I(S_i + C_i \ge t)dN_i^o(t)$. The estimation of model (2.1) will be based on targeting to minimize the following objective function:

$$
\begin{aligned}
l(\beta, \gamma) \;=\; & \sum_{i=1}^{n} R_i \int_0^{\tau} W(u)\{Y_i(u) - \beta^T(u)X_i(u) - \gamma^T Z_i(u)\}^2 \, dN_i^c(u) \\
& + \sum_{i=1}^{n} (1 - R_i)\widehat{E}_S\bigg\{ \int_0^{\tau} W(u)\{Y_i(u) - \beta^T(u)X_i(u) \\
& - \gamma^T Z_i(u)\}^2 \, dN_i^c(u)|\mathcal{X}\bigg\}, \qquad (2.3)
\end{aligned}
$$

where $W(\cdot)$ is a nonnegative weight function, and $\widehat{E}_S\{\cdot|\mathcal{X}\}$ is the estimate of the conditional expectation, $E_S\{\cdot|\mathcal{X}\}$, of a function of S_i given $\mathcal{X}$. For $R_i = 0$ and a smooth random function $G_n(t, X_i(t), Z_i(t), Y_i(t))$, $\widehat{E}_S\left\{\int_0^{\tau} G_n(u, X_i(u), Z_i(u), Y_i(u))dN_i^c(u)|\mathcal{X}\right\}$ equals

$$
\sum_{j=1}^{n_i} \widehat{E}_S\{G_n(S_i + T_{ij}, X_i(T_{ij}^o), Z_i(T_{ij}^o), Y_i(T_{ij}^o))I(C_i \ge T_{ij})I(S_i + T_{ij} \le \tau)|\mathcal{X}\}
$$

$$= \sum_{j=1}^{n_i} \widehat{E}_S\{G_n(S_i+T_{ij}, X_{ij}, Z_{ij}, Y_{ij})I(C_i \geq T_{ij})I(S_i+T_{ij} \leq \tau)|\mathcal{X}\}$$

$$= \sum_{j=1}^{n_i} \int_0^\infty G_n(s+T_{ij}, X_{ij}, Z_{ij}, Y_{ij})I(C_i \geq T_{ij})I(s+T_{ij} \leq \tau)\, d\widehat{F}_S(s|\mathcal{X})$$

Since the observations for different subjects are independent, the above equation equals

$$\begin{aligned}
&\sum_{j=1}^{n_i} \int_0^\infty G_n(s+T_{ij}, X_{ij}, Z_{ij}, Y_{ij})I(C_i \geq T_{ij})I(s+T_{ij} \leq \tau)\, d\widehat{F}_S(s|\mathcal{X}_i) \\
= &\sum_{j=1}^{n_i} \int_0^\infty G_n(s+T_{ij}, X_{ij}, Z_{ij}, Y_{ij})I(C_i \geq T_{ij})I(s+T_{ij} \leq \tau)\, d\widehat{F}_S(s|\mathcal{D}_i, R_i = 0) \\
= &\sum_{j=1}^{n_i} \int_0^\infty G_n(s+T_{ij}, X_{ij}, Z_{ij}, Y_{ij})I(C_i \geq T_{ij})I(T_{ij} \leq \tau - s)I(s < V_i)\, \frac{d\widehat{F}_S(s|\mathcal{D}_i)}{\widehat{F}_S(V_i|\mathcal{D}_i)}.
\end{aligned} \tag{2.4}$$

Note that the function $G_n(u, X_i(u), Y_i(u), Z_i(u))$ maybe depend on the observed data which makes it measurable with respect to $\mathcal{X}$ for each fixed $(u, X_i(u), Y_i(u), Z_i(u))$.

For fixed γ and at time t, we estimate $\beta(t)$ by minimizing

$$\tilde{l}_t(\beta, \gamma) = \sum_{i=1}^{n} \ll \int_0^\tau K_h(u-t)\{Y_i(u) - \beta^T X_i(u) - \gamma^T Z_i(u)\}^2\, dN_i^c(u) \gg_R, \tag{2.5}$$

where and hereafter, the notation $\ll H_i(t) \gg_R = R_i H_i(t) + (1-R_i)\widehat{E}_S\{H_i(t)|\mathcal{X}\}$ is used for a random function $H_i(t)$, and $K_h(t) = h^{-1}K(t/h)$, $K(t)$ is a symmetric kernel function with a compact support and h is the bandwidth depending on n.

Taking derivative of $\tilde{l}_t(\beta, \gamma)$ with respect to β for a fixed γ yields

$$\frac{\partial l_t(\beta, \gamma)}{\partial \beta} = -2\sum_{i=1}^{n} \ll \int_0^\tau K_h(u-t)X_i(u)\{Y_i(u) - \beta^T X_i(u) - \gamma^T Z_i(u)\}\, dN_i^c(u) \gg_R, \tag{2.6}$$

This leads to the following estimating function

$$U_t(\beta, \gamma) = \sum_{i=1}^{n} \ll \int_0^\tau K_h(u-t)X_i(u)\{Y_i(u) - \beta^T X_i(u) - \gamma^T Z_i(u)\}\, dN_i^c(u) \gg_R . \tag{2.7}$$

The root of the equation $U_t(\beta, \gamma) = 0$ is denoted by $\tilde{\beta}(t, \gamma)$. Let $\tilde{E}_{zx}(t) = n^{-1} \sum_{i=1}^n \ll \int_0^\tau K_h(u-t) Z_i(u) X_i^T(u)\, dN_i^c(u) \gg_R$. The $\tilde{E}_{yx}(t)$ and $\tilde{E}_{xx}(t)$ are similarly defined by replacing Z_i with Y_i and X_i respectively. The local least squares estimator for $\beta(t)$ for fixed γ is then given by

$$\tilde{\beta}(t; \gamma) = \tilde{Y}_x^T(t) - \tilde{Z}_x^T(t)\gamma, \tag{2.8}$$

where $\tilde{Y}_x(t) = \tilde{E}_{yx}(t)(\tilde{E}_{xx}(t))^{-1}$ and $\tilde{Z}_x(t) = \tilde{E}_{zx}(t)(\tilde{E}_{xx}(t))^{-1}$. Replacing $\tilde{\beta}(t;\gamma)$ for $\beta(t)$ in (2.3) and taking derivative with respect to γ, we obtain the profile estimating equation for γ:

$$\begin{aligned} U(\gamma) &= \sum_{i=1}^n \int_{t_1}^{t_2} \ll W(t)\{Z_i(t) - \tilde{Z}_x(t) X_i(t)\}\{Y_i(t) - X_i^T(t)\tilde{\beta}(t;\gamma) \\ &\qquad -Z_i^T(t)\gamma\}\, dN_i^c(t) \gg_R = 0. \end{aligned} \tag{2.9}$$

Here $[t_1, t_2]$ is taken as a subinterval of $[0, \tau]$ to avoid boundary problems in the theoretical justifications. In practice, $[t_1, t_2]$ can be taken as $[0, \tau]$. From (2.9), we solve for γ to get $\widehat{\gamma}$ which equals $\widehat{D}^{-1}\widehat{W}$ where

$$\begin{aligned} \widehat{D} &= n^{-1} \sum_{i=1}^n \int_{t_1}^{t_2} \ll W(t)\{Z_i(t) - \tilde{Z}_x(t) X_i(t)\}^{\otimes 2} dN_i^c(t) \gg_R \\ \widehat{W} &= n^{-1} \sum_{i=1}^n \int_{t_1}^{t_2} \ll W(t)\{Z_i(t) - \tilde{Z}_x(t) X_i(t)\}\{Y_i(t) - X_i^T(t)\tilde{Y}_x^T(t)\} dN_i^c(t) \gg_R . \end{aligned}$$

An estimator of $\beta(t)$ is given by $\widehat{\beta}(t) = \tilde{\beta}(t; \widehat{\gamma})$.

When S_i is observed for all subjects, $R_i = 1$. The estimators for $\beta(t)$ and γ are reduced to those under Sun and Wu (2005). However, when S_i is censored, the estimating equations (2.6) and (2.9) are weighted according to the conditional distribution of S_i so that the estimated covariate effects correspond to those at the time since the actual time origin. A key factor for this procedure to work is that the censoring time V_i is observed for all subjects so that the estimation of $F_S(s \mid \mathcal{D}_i, R_i = 0)$ is possible.

2.3 Computational algorithm

The boundary effects on the estimation of $\beta(t)$ and the covariance matrix of its estimator can be reduced by applying the equivalent kernel for the local linear approach; see Fan & Gijbels (1996).

Suppose the binary data $(T_1, B_1), (T_2, B_2), \cdots, (T_n, B_n)$ which are n independent and identically distributed copies from (T, B). To estimate $m(t_0) = E(B|T = t_0)$ is of interest. Suppose we use symmetric kernel $K(x)$ in local constant method. Then the local constant estimator of $m(t)$ at point t_0 will be

$$\widehat{m}_C = \frac{n^{-1}\sum_{i=1}^{n} K_h(T_i - t_0)B_i}{n^{-1}\sum_{i=1}^{n} K_h(T_i - t_0)}.$$

To get the equivalent kernel, we will mimic some notations in Fan & Gijbels (1996).

$$S_{n,j}(t_0) = \sum_{i=1}^{n} K_h(T_i - t_0)(T_i - t_0)^j, \ j = 0, 1, 2.$$

Then

$$S_n(t_0) = \begin{pmatrix} S_{n,0}(t_0) & S_{n,1}(t_0) \\ S_{n,1}(t_0) & S_{n,2}(t_0) \end{pmatrix}.$$

Meanwhile the inverse can be written as

$$S_n^{-1}(t_0) = \frac{1}{S_{n,0}(t_0)S_{n,2}(t_0) - S_{n,1}^2(t_0)} \begin{pmatrix} S_{n,2}(t_0) & -S_{n,1}(t_0) \\ -S_{n,1}(t_0) & S_{n,0}(t_0) \end{pmatrix}.$$

As stated in the Section 3.2.2 of Fan & Gijbels (1996), the equivalent kernel for local linear approach is

$$K_h^*(t - t_0) = e_1^T S_n^{-1}(t_0)(1 \ \ t - t_0)^T K_h(t - t_0),$$

where $e_1 = (1 \ \ 0)^T$. Then we can simplify the equivalent kernel as follows.

$$K_h^*(t - t_0) \ = \ e_1^T S_n^{-1}(t_0)(1 \ \ t - t_0)^T K_h(t - t_0)$$

$$
\begin{aligned}
&= \frac{K_h(t-t_0)(\begin{array}{cc} 1 & 0 \end{array})}{S_{n,0}(t_0)S_{n,2}(t_0)-S_{n,1}^2(t_0)} \begin{pmatrix} S_{n,2}(t_0) & -S_{n,1}(t_0) \\ -S_{n,1}(t_0) & S_{n,0}(t_0) \end{pmatrix} \begin{pmatrix} 1 \\ t-t_0 \end{pmatrix} \\
&= \frac{\{S_{n,2}(t_0)-S_{n,1}(t_0)(t-t_0)\}K_h(t-t_0)}{S_{n,0}(t_0)S_{n,2}(t_0)-S_{n,1}^2(t_0)}.
\end{aligned}
$$

Therefore, the local linear estimator $\widehat{m}_L$ at point t_0 under the model $B = m(T) + \epsilon$ is

$$
\frac{n^{-1}\sum_{i=1}^n K_h^*(T_i-t_0)B_i}{n^{-1}\sum_{i=1}^n K_h^*(T_i-t_0)} = \frac{\sum_{i=1}^n\{S_{n,2}(t_0)-S_{n,1}(t_0)(T_i-t_0)\}K_h(T_i-t_0)B_i}{\sum_{i=1}^n\{S_{n,2}(t_0)-S_{n,1}(t_0)(T_i-t_0)\}K_h(T_i-t_0)}.
$$

Compared to the local constant estimator above, if we use the following kernel

$$
W_h(T_i-t_0) = \{S_{n,2}(t_0)-S_{n,1}(t_0)(T_i-t_0)\}K_h(T_i-t_0) \tag{2.10}
$$

instead of $K_h(T_i - t_0)$, we simply obtain the local linear estimator.

Let $f(t)$ be the density function of T. For a interior point t_0, the local linear estimator is asymptotically equivalent to the local constant estimator as $h \to 0$ and $nh^5 = O(1)$ since for a symmetric kernel, $\int K(x)x\,dx = 0$. Then

$$
\begin{aligned}
n^{-1}ES_{n,j}(t_0) &= EK_h(T_i-t_0)(T_i-t_0)^j = \int K_h(t-t_0)(t-t_0)^j f(t)\,dt \\
&= \int K(x)h^j x^j f(t_0+hx)\,dx = h^j(f(t_0)+o(h))\int K(x)x^j\,dx = o(h).
\end{aligned}
$$

Especially note that $n^{-1}ES_{n,1}(t_0) = 0$. Hence

$$
\begin{aligned}
\widehat{m}_L &= \frac{\sum_{i=1}^n\{S_{n,2}(t_0)-S_{n,1}(t_0)(T_i-t_0)\}K_h(T_i-t_0)B_i}{\sum_{i=1}^n\{S_{n,2}(t_0)-S_{n,1}(t_0)(T_i-t_0)\}K_h(T_i-t_0)} \\
&= \frac{n^{-1}\sum_{i=1}^n\{n^{-1}S_{n,2}(t_0)-n^{-1}S_{n,1}(t_0)h\frac{T_i-t_0}{h}\}K_h(T_i-t_0)B_i}{n^{-1}\sum_{i=1}^n\{n^{-1}S_{n,2}(t_0)-n^{-1}S_{n,1}(t_0)h\frac{T_i-t_0}{h}\}K_h(T_i-t_0)} \\
&\approx \frac{n^{-1}\sum_{i=1}^n K_h(T_i-t_0)B_i}{n^{-1}\sum_{i=1}^n K_h(T_i-t_0)} + o_p(h^2) \\
&= \widehat{m}_C + o_p(h^2).
\end{aligned}
$$

Hence $(nh)^{1/2}(\widehat{m}_L - \widehat{m}_C) = o_p((nh^5)^{1/2})$, which means the asymptotic distributions for the local linear estimator and the local constant estimator are the same for an interior point t_0 as $h \to 0$ and $nh^5 = O(1)$. This enables using the equivalent kernel for the boundary time points while using the kernel in local constant approach for the interior time points.

In estimating $\beta(t)$, time points T may be unknown since S_i is left censored by V_i. Then we cannot simply use $S_{n,j}(t_0)$ defined above. Let

$$S_{n,j}(t) = \sum_{i=1}^{n} \ll \int_0^{\tau} K_h(u-t)(u-t)^j dN_i^c(u) \gg_R, \ j = 0, 1, 2.$$

Now under the new definition of $S_{n,j}(t_0)$, we still have the form of equivalent kernel in (2.10) for local linear approach of estimating $\beta(t)$.

2.4 Cross-validation bandwidth selection

The optimal theoretical bandwidth is difficult to achieve since it would involve estimating the second derivative of $\beta(t)$ with respect to t, $\beta''(t)$; see Fan and Gijbels (1996) and Cai and Sun (2002). In practice, the appropriate bandwidth selection can be based on a cross-validation method. This approach is widely used in nonparametric function estimation literature; see Rice and Silverman (1991) for leave-one-subject-out cross-validation approach and Tian, Zucker and Wei (2005) for K-fold cross-validation approach.

An analog of the K-fold cross-validation approach in the current setting is to divide the data into K equal-sized groups. Let D_k denote the kth subgroup of data, then the kth prediction error is given by

$$PE_k(h) = \sum_{i \in D_k} \ll \int_{t_1}^{t_2} \left[Y_i(t) - (\widehat{\beta}_{(-k)}(t))^T X_i(t) - \widehat{\gamma}_{(-k)}^T Z_i(t) \right]^2 dN_i^c(t) \gg_R, \quad (2.11)$$

for $k = 1, \ldots, K$, where $\widehat{\beta}_{(-k)}(t)$ and $\widehat{\gamma}_{(-k)}$ are the estimators of $\beta(t)$ and γ based on the data without the subgroup D_k. The data-driven bandwidth selection based on the K-fold cross-validation is to choose the bandwidth h that minimizes the total prediction error $PE(h) = \sum_{k=1}^{K} PE_k(h)$. This bandwidth selection procedure will be further studied and tested empirically through simulations.

CHAPTER 3: ASYMPTOTIC PROPERTIES

In this section we will explore the asymptotic properties of the proposed estimators. For simplicity, the asymptotic results are derived assuming that S_i is independent of $\mathcal{D}_i$. In general, the Cox model can be used to model the conditional hazard function of S_i depending on $\mathcal{D}_i$. The proofs can be modified to accommodate this situation. First we will introduce some notations. Let

$$e_{zx}(t) = E(\xi_i(t)\alpha_i(t)Z_i(t)X_i^T(t)),$$

where $\xi_i(t) = I(S_i+C_i+c_1 \geq t)$ and $\alpha_i(t)$ is the conditional mean rate of $N_i^o(t)$ defined in (2.2). $e_{xx}(t)$ and $e_{yx}(t)$ are similarly defined. Let $y_x(t) = e_{yx}(t)(e_{xx}(t))^{-1}$ and $z_x(t) = e_{zx}(t)(e_{xx}(t))^{-1}$. Let γ_0 and $\beta_0(t)$ be the true values of γ and $\beta(t)$ respectively. Let $F_v(t)$ be the distribution function of V_i and $f_s(t)$ be the density function of S_i. In additional to the conditional independence assumptions and noninformative censoring assumptions stated in Section 2.1 we assume the following conditions for the asymptotic results to hold.

Conditions (I). Assume that the $\{n_i\}$ are bounded; the $\{S_i\}$ are bounded by a large enough value L and independent of $\mathcal{D}_i$; the kernel function $K(\cdot)$ is symmetric with compact support on $[-1, 1]$; the processes $X_i(t)$, $Z_i(t)$ and $\alpha_i(t)$, $0 \leq t \leq \tau$, are bounded by a constant, continuous and their total variations are bounded by a constant; the values of the jth measurement X_{ij} and Z_{ij} are also bounded; the processes $X_i(t)$, $Z_i(t)$ and $Y_i(t)$ are left continuous processes; $(e_{xx}(t))^{-1}$ for $0 \leq t \leq \tau$ are bounded; the weight function $W(t)$ can be written as a difference of two monotone functions and each converges to a deterministic function so that $W(t)$ converges to

$w(t)$.

Conditions (II). Define $\tau_H = \sup_s\{s: F_v(L-s)F_s(L-s) > 0\}$. Assume

$$\int_0^{\tau_H} \frac{f_s(L-s)}{F_v(L-s)}\, ds < \infty.$$

Also assume that $F_s(s_0) > 0$ and $F_v(s_0) = 0$ for some $s_0 > 0$.

Under Conditions (II), the consistency and weak convergence of the Kaplan Meier estimation for the distribution of S_i can be extended to the whole line (Ying (1989)). Under Conditions (I) and (II), it follows from Lemma A.2.3 that $\tilde{E}_{zx}(t) \xrightarrow{P} e_{zx}(t)$ uniformly in $t \in [t_1, t_2] \subset [0, \tau]$. Similar asymptotic results hold for $\tilde{E}_{yx}(t)$ and $\tilde{E}_{xx}(t)$. By continuous mapping theorem, the above results lead to the conclusion that $\tilde{Y}_x(t)$ and $\tilde{Z}_x(t)$ converge to $y_x(t)$ and $z_x(t)$ uniformly in $t \in [t_1, t_2]$ respectively.

Theorem 3.1 and Theorem 3.2 state that both the estimators $\widehat{\gamma}$ and $\widehat{\beta}(t)$ are consistent. Note that $\widehat{\gamma}$ is the minimizer of $n^{-1}\tilde{l}(\gamma) = n^{-1}l(\tilde{\beta}(\cdot;\gamma), \gamma)$ which equals

$$n^{-1}\sum_{i=1}^{n} \ll \int_0^{\tau} W(s)\{Y_i(s) - \tilde{Y}_x(s)X_i(s) + \gamma^T(\tilde{Z}_x(s)X_i(s) - Z_i(s))\}^2\, dN_i^c(s) \gg_R .$$

In the proof of Theorem 3.1, we show that $n^{-1}\tilde{l}(\gamma)$ converges uniformly to a deterministic function of γ that minimizes at $\gamma = \gamma_0$. Then the consistency of $\widehat{\gamma}$ follows by Theorem 5.7 of van der Vaart (1998).

Theorem 3.1: (Consistency of $\widehat{\gamma}$) Under Conditions (I) and (II), $\widehat{\gamma} = \widehat{D}^{-1}\widehat{W}$ converges to its true value γ_0 in probability as $n \to \infty$.

The consistency of $\widehat{\beta}(t)$ follows from Lemma A.2.3 and Theorem 3.1,

$$\begin{aligned}
\widehat{\beta}(t) &= \tilde{Y}_x^T(t) - \tilde{Z}_x^T(t)\widehat{\gamma} \xrightarrow{P} y_x^T(t) - z_x^T(t)\gamma_0 \\
&= (e_{xx}(t))^{-1}e_{yx}^T(t) - (e_{xx}(t))^{-1}e_{zx}^T(t)\gamma_0 \\
&= (e_{xx}(t))^{-1}[E(\xi_i(t)\alpha_i(t)X_i(t)Y_i^T(t)) - E(\xi_i(t)\alpha_i(t)X_i(t)Z_i^T(t))\gamma_0] \\
&= (e_{xx}(t))^{-1}E(\xi_i(t)\alpha_i(t)X_i(t)[Y_i^T(t) - Z_i^T(t)\gamma_0]) \\
&= (e_{xx}(t))^{-1}E(\xi_i(t)\alpha_i(t)X_i(t)[X_i^T(t)\beta_0(t) + \epsilon^T(t)])
\end{aligned}$$

$$= (e_{xx}(t))^{-1}e_{xx}(t)\beta_0(t) + E(E[\xi_i(t)\alpha_i(t)X_i(t)\epsilon^T(t) \mid X_i(t), Z_i(t), S_i + C_i \geq t])$$
$$= \beta_0(t) + E(\xi_i(t)\alpha_i(t)X_i(t)E[\epsilon^T(t) \mid X_i(t), Z_i(t), S_i + C_i \geq t])$$
$$= \beta_0(t) + E(\xi_i(t)\alpha_i(t)X_i(t)E[\epsilon^T(t) \mid X_i(t), Z_i(t)]) = \beta_0(t).$$

Theorem 3.2: (Consistency of $\widehat{\beta}(t)$) Under Conditions (I) and (II), $\widehat{\beta}(t) = \tilde{\beta}(t;\widehat{\gamma})$ converges to $\beta_0(t)$ in probability uniformly on $[t_1, t_2]$ as $n \to \infty$, where $0 \leq t_1 \leq t_2 \leq \tau$.

The details of the proofs of Theorem 3.1 and 3.2 are given in the Appendix A.3.

In Section 2.2, $\widehat{\gamma}$ is the solution of (2.9). So denote $U(\gamma)$ as

$$\sum_{i=1}^{n} \int_{t_1}^{t_2} \ll W(t)\{Z_i(t) - \tilde{Z}_x(t)X_i(t)\}\{Y_i(t) - X_i^T(t)\tilde{\beta}(t;\gamma) - Z_i^T(t)\gamma\}\, dN_i^c(t) \gg_R$$

which is usually called the score function. Then the Taylor expansion of $U(\widehat{\gamma})$ at γ_0 is

$$n^{1/2}(\widehat{\gamma} - \gamma_0) = -\left(n^{-1}\frac{\partial U(\gamma^*)}{\partial \gamma^T}\right)^{-1}[n^{-1/2}U(\gamma_0)],$$

where γ^* is on the line segment between $\widehat{\gamma}$ and γ_0. To prove the asymptotic normality of $n^{1/2}(\widehat{\gamma}-\gamma_0)$, it is sufficient to prove the convergence in probability to a non-singular matrix of $n^{-1}\frac{\partial U(\gamma^*)}{\partial \gamma^T}$, and the weak convergence of $n^{-1/2}U(\gamma_0)$. The convergence in probability can be easily obtained by applying Lemma A.2.2. And $n^{-1/2}U(\gamma_0)$ can be derived to equal to

$$n^{-1/2}\sum_{i=1}^{n}\int_{t_1}^{t_2} w(t)\{Z_i(t) - z_x(t)X_i(t)\}\epsilon_i(t)[R_i dN_i^c(t) + E_s\{(1-R_i)dN_i^c(t) \mid \mathcal{D}_i, R_i = 0\}] + o_p(1).$$

Then applying theorem 5.21 (van der Vaart, 1998) to the sore function, the asymptotic normality of $\widehat{\gamma}$ is presented in the following theorem.

Theorem 3.3: (Asymptotic Normality of $\widehat{\gamma}$) Under Conditions (I) and (II), $n^{1/2}(\widehat{\gamma} -$

$\gamma_0) \xrightarrow{D} \mathcal{N}(0, D^{-1}VD^{-1})$ as $n \to \infty$ where

$$D = E\bigg(\int_{t_1}^{t_2} w(t)\{Z_i(t) - z_x(t)X_i(t)\}^{\otimes 2}\, dN_i^c(t)\bigg),$$
$$V = E\bigg\{\int_{t_1}^{t_2}[R_i w(t)(Z_i(t) - z_x(t)X_i(t))\epsilon_i(t)dN_i^c(t)$$
$$+(1-R_i)E_s\{w(t)(Z_i(t) - z_x(t)X_i(t))\epsilon_i(t)dN_i^c(t) \mid \mathcal{D}_i, R_i = 0\}]\bigg\}^{\otimes 2}.$$

The matrix V can be reformulated to assist the understanding and interpretation. Let $\tilde{Q}_i = \int_{t_1}^{t_2} w(t)(Z_i(t) - z_x(t)X_i(t))\epsilon_i(t)dN_i^c(t)$. Then $V = Var\{R_i\tilde{Q}_i + (1 - R_i)E_s(\tilde{Q}_i \mid \mathcal{D}_i, R_i = 0)\}$. Under the assumptions in Section 2.1, $E(\tilde{Q}_i \mid R_i = 1)$ equals

$$\begin{aligned} & E[E\{\tilde{Q}_i \mid R_i = 1, X_i(\cdot), Z_i(\cdot), N_i(\cdot), S_i, V_i, C_i\} \mid R_i = 1] \\ = \;& E\bigg[\int_{t_1}^{t_2} w(t)(Z_i(t) - z_x(t)X_i(t))E\{\epsilon_i(t) \mid X_i(\cdot), Z_i(\cdot)\}dN_i^c(t) \mid R_i = 1\bigg] = 0. \end{aligned}$$

Similarly, $E(\tilde{Q}_i \mid R_i = 0) = 0$. Hence,

$$\begin{aligned} & R_i\tilde{Q}_i + (1-R_i)E_s(\tilde{Q}_i \mid \mathcal{D}_i, R_i = 0) \\ = \;& R_i\{\tilde{Q}_i - E_s(\tilde{Q}_i \mid R_i = 1)\} + (1-R_i)\{E_s(\tilde{Q}_i \mid \mathcal{D}_i, R_i = 0) - E_s(\tilde{Q}_i \mid R_i = 0)\} \\ \triangleq \;& Q_1 + Q_2. \end{aligned}$$

By the fact that $EQ_1 = 0$, $EQ_2 = 0$, and Q_1 and Q_2 are uncorrelated, $Var\{R_i\tilde{Q}_i + (1 - R_i)E_s(\tilde{Q}_i \mid \mathcal{D}_i, R_i = 0)\} = Var(Q_1) + Var(Q_2)$, $Var(Q_1) = P(R_i = 1)Var(\tilde{Q}_i \mid R_i = 1)$ and $Var(Q_2) = P(R_i = 0)Var\{E(\tilde{Q}_i \mid \mathcal{D}_i, R_i = 0\}$. Hence, we have

$$\begin{aligned} V &= Var\{R_i\tilde{Q}_i + (1-R_i)E_s(\tilde{Q}_i \mid \mathcal{D}_i, R_i = 0)\} \\ &= P(R_i = 1)Var(\tilde{Q}_i \mid R_i = 1) + P(R_i = 0)Var\{E(\tilde{Q}_i \mid \mathcal{D}_i, R_i = 0\}. \end{aligned}$$

Based on the equations (A.33) and (A.44), the asymptotic variance in the statement of theorem can be estimated by $n^{-1}\widehat{D}^{-1}\widehat{V}\widehat{D}^{-1}$ where

$$\widehat{D} = n^{-1}\sum_{i=1}^{n}\int_{t_1}^{t_2} \ll W(t)\{Z_i(t) - \tilde{Z}_x(t)X_i(t)\}^{\otimes 2}\, dN_i^c(t) \gg_R,$$

$$\widehat{V} = n^{-1} \sum_{i=1}^{n} \left\{ \int_{t_1}^{t_2} \ll W(t)(Z_i(t) - \tilde{Z}_x(t)X_i(t))\widehat{\epsilon}_i(t)\, dN_i^c(t) \gg_R \right\}^{\otimes 2}$$

and $\widehat{\epsilon}_i(t) = Y_i(t) - \widehat{\beta}(t)^T X_i(t) - \widehat{\gamma}^T Z_i(t)$. This estimator is consistent estimator of the asymptotic variance by the consistency of $\widehat{D}$ and $\widehat{V}$. The proof of Theorem 3.3 is given in the Appendix A.3.

Before demonstrating the asymptotic normality of $\widehat{\beta}(t)$ at each fixed time point t, we first introduce the following notations. Let the filtration $\mathcal{F}_t^R = \sigma\ \{R_i N_i^c(s),\ (1 - R_i)E(N_i^c(s) \mid \mathcal{D}_i, R_i = 0), R_i, X_i(s), Z_i(s), Y_i(s), 0 \le s \le t, 1 \le i \le n\}$. Let

$$dN_i^R(t) = R_i dN_i^c(t) + (1 - R_i)E(dN_i^c(t) \mid \mathcal{D}_i, R_i = 0),$$

and

$$\begin{aligned} \alpha_i^R(t)dt &= E\{dN_i^R(t) \mid \mathcal{F}_{t-}^R\} \\ &= E\{R_i dN_i^c(t) + (1 - R_i)E(dN_i^c(t) \mid \mathcal{D}_i, R_i = 0) \mid \mathcal{F}_{t-}^R\}. \end{aligned} \tag{3.1}$$

Also let $dM_i^R(t) = dN_i^R(t) - \alpha_i^R(t)dt$. Then $M_i^R(t)$ is a $\mathcal{F}_t^R-$martingale, with the predictable variation process $\int_0^t Var\{dM_i^R(s) \mid \mathcal{F}_{s-}^R\} = \int_0^t \alpha_i^R(s)ds$.

Then the asymptotic normality of $\widehat{\beta}(t)$ is given in the following theorem and its proof is given in the Appendix A.3.

Theorem 3.4: (Asymptotic Normality of $\widehat{\beta}(t)$) Under Conditions (I) and (II), $((nh)^{1/2}(\widehat{\beta}(t) - \beta_0(t) - \beta_{Bias}(t)) \xrightarrow{D} \mathcal{N}(0, \mu_0 \Sigma(t))$ for each fixed time point t as $n \to \infty$, $h \to 0$, $nh^2 \to \infty$ and $nh^5 = O(1)$. Here $\mu_0 = \int_{-1}^1 K^2(u)du$, $\mu_2 = \int_{-1}^1 u^2 K^2(u)du$,

$$\begin{aligned} \beta_{Bias}(t) &= (1/2)\mu_2 h^2 (e_{xx}(t))^{-1}\{e''_{xy}(t) - e''_{xz}(t)\gamma_0 - e''_{xx}(t)\beta_0(t)\}, \\ \Sigma(t) &= (e_{xx}(t))^{-1} E\{\epsilon_i^2(t)\alpha_i^R(t)X_i(t)X_i^T(t)\}(e_{xx}(t))^{-1}. \end{aligned}$$

Based on the equation (A.52), the covariance matrix of $\widehat{\beta}(t)$ can be estimated by

$$n^{-2}(\tilde{E}_{xx}(t))^{-1}\Bigg[\sum_{i=1}^{n}\Bigg(\ll \int_0^\tau K_h(u-t)X_i(u)\widehat{\epsilon}_i(u)dN_i^c(u) \gg_R\Bigg)^{\otimes 2}\Bigg](\tilde{E}_{xx}(t))^{-1},$$

which is a consistent estimator based on the derivation in the Appendix A.3.

Note that

$$\begin{aligned}
& (nh)^{1/2}(\widehat{\beta}(t)-\beta_0(t)-\beta_{Bias}(t)) \\
= \; & (nh)^{1/2}(\tilde{\beta}(t;\gamma_0)-\beta_0(t)-\beta_{Bias}(t))+(nh)^{1/2}(\widehat{\gamma}-\gamma_0)\frac{\partial\tilde{\beta}(t;\gamma_0)}{\partial\gamma}+O_p(n^{-1/2}h^{1/2}) \\
= \; & n^{-1/2}\sum_{i=1}^{n}h^{1/2}\Bigg[(e_{xx}(t))^{-1}\Bigg(R_i\int_0^\tau K_h(u-t)X_i(u)\epsilon_i(u)dN_i^c(u) \\
& \qquad +(1-R_i)E_s\Big\{\int_0^\tau K_h(u-t)X_i(u)\epsilon_i(u)dN_i^c(u)\mid\mathcal{D}_i,R_i=0\Big\}\Bigg) \\
& \qquad -D^{-1}\Bigg(\int_{t_1}^{t_2} w(t)\{Z_i(t)-z_x(t)X_i(t)\}\epsilon_i(t)[R_i dN_i^c(t) \\
& \qquad +E_s\{(1-R_i)dN_i^c(t)\mid\mathcal{D}_i,R_i=0\}]\Bigg)\tilde{z}_x(t)\Bigg] \\
& +O(h^{1/2})+o_p(h^{1/2})+O_p(n^{-1/2}h^{5/2})+O_p(n^{-1/2}h^{1/2}).
\end{aligned}$$

An adjusted estimation of the covariance matrix of $\widehat{\beta}(t)$ is given as

$$\begin{aligned}
& n^{-2}\sum_{i=1}^{n}\Bigg((\tilde{E}_{xx}(t))^{-1}\ll\int_0^\tau K_h(u-t)X_i(u)\widehat{\epsilon}_i(u)dN_i^c(u)\gg_R \\
& \qquad -\widehat{D}^{-1}\ll\int_{t_1}^{t_2} W(t)\{Z_i(t)-\tilde{Z}_x(t)X_i(t)\}\widehat{\epsilon}_i(t)dN_i^c(t)\gg_R\tilde{Z}_x(t)\Bigg)^{\otimes 2}.
\end{aligned} \tag{3.2}$$

We will use the adjusted estimated covariance matrix in the following simulation and real data application.

CHAPTER 4: A SIMULATION STUDY

A numerical study is conducted to illustrate the feasibility and validity of the proposed methods. The performances of the estimator for γ are measured through the bias (Bias), the sample standard error of the estimates (SSE), the estimated standard error of $\widehat{\gamma}$(ESE) and the coverage probability of a 95% confidence interval for γ. The overall performance of the estimator for the jth component $\beta_j(\cdot)$ on the interval $[0, \tau]$ is evaluated through the square root of integrated average square error

$$RASE(\widehat{\beta}_j(\cdot)) = \left\{ \frac{1}{\tau} \int_0^\tau (\widehat{\beta}_j(t) - \beta_j(t))^2 \, dt) \right\}^{1/2},$$

where $\widehat{\beta}_j(t)$ is the estimate of $\beta_j(t)$. The simulation uses the unit weight function. The interval $[t_1, t_2] = [0.15, \pi]$ is taken to be $[0, \tau]$ in the estimating functions (2.9).

The performance of the proposed estimators are examined under the following selected setting of model (2.1). Let $Y_i(t)$ follow the semiparametric additive model:

$$Y_i(t) = \beta_0(t) + \beta_1(t) X_i + \gamma Z_i + \epsilon_i(t), \qquad i = 1, \ldots, n, \tag{4.1}$$

where $\beta_0(t) = 1 - t$, $\beta_1(t) = 5\sin(t)$, $\gamma = 8$, X_i is uniformly distributed on $[0, 1]$, and Z_i is a Bernoulli random variable with $P(Z_i = 1) = 0.5$. The error process $\epsilon_i(t)$ has a normal distribution with mean ϕ_i and variance 1 for subject i where ϕ_i follows a standard normal distribution.

For subject i, S_i is generated from the uniform distribution on $[0, 0.8]$. The first sampling point is set as $T_{i1} = 0$, and the rest T_{ij}'s are generated from a Poisson process $N_i(t)$ with the intensity rate of $\lambda_0 \exp(\eta_1 X_i + \eta_2 Z_i)$ where $\lambda_0 = 0.4$, $\eta_1 = 1$ and $\eta_2 = 0.3$. Let Y_{ij} be the responses $Y_i(t)$ at time points $T^o_{ij} = T_{ij} + S_i$ following model

(4.1). The censoring time C_i is exponentially distributed with the parameter adjusted to give an approximately 0% or 30% censoring in the time interval $[0, \tau] = [0, 4]$, which is the probability of $\max_{1 \le j \le n_i}\{T^o_{ij} \wedge \tau\} > S_i + C_i$, denoted as c_R. The average number of observations in the interval $[0, \tau] = [0, 4]$ per subject is about 3.48.

The following four cases, including three different left censoring percentages for S_i,denoted as c_L, and the one that ignores S_i by mistreating T_{ij} as the measurement times since the actual time origin, are conducted to examine the behavior of both estimators: (1) $c_L = 0\%$ which means $\{S_i\}$ are observed for all the subjects; (2) $c_L = 20\%$; (3) $c_L = 50\%$; and (4) the last case treats T_{ij} as the time since the actual time origin and $Y_{ij} = Y_i(T^o_{ij})$ as the response at $t = T_{ij}$. The censoring time V_i is generated from an uniform distribution $[a, b]$ with the parameters a and b adjusted to yield desired percentages of left censoring for S_i.

The simulation presented in the following is carried out using local linear approach. As discussed in Section 2.3, to reduce the time consumption of simulations, the Epanechnikov kernel $K(u) = 0.75(1 - u^2)I(|u| \le 1)$ is used for the inner points of time interval, i.e. $(3h, \tau - 3h)$ while the equivalent kernel in (2.10) is applied for the boundary points in $[0, 3h] \bigcup [\tau - 3h, \tau]$.

For sample sizes $n = 200$, 300 and 500, and bandwidths $h = 0.3$, 0.4 and 0.5, Table 4.1 shows the biases (Bias), the sample standard errors (SSE), the estimated standard errors (ESE) of $\widehat{\gamma}$, the coverage probabilities of a 95% confidence interval for γ and also the square root of integrated average square error (RASE) of both components of $\widehat{\beta}(t)$ for the first three cases based on 500 simulations when there is no right censoring. While Table 4.2 shows the same criterions for the first three cases based on 500 simulations when there is 30% of subjects right-censored during the time scale. The biases of $\widehat{\gamma}$ for the first three cases using the proposed method are small. The sample standard errors of $\widehat{\gamma}$ are close to its estimated standard errors. Both standard errors reduce as the sample size increases. When the left censoring percentage of S_i goes up, the standard errors rise a tiny bit since the increase of percentage means more unknown information of S_i. The coverage probabilities of $\widehat{\gamma}$ are slightly around 0.95 as expected. The square root of integrated average square error of $\widehat{\beta}_0(t)$ is smaller than that of $\widehat{\beta}_1(t)$ because $\beta_0(t)$ is a straight line while $\beta_1(t)$ is more curvy. Both RASE's increase together with the left censoring percentage of S_i. Furthermore, as the bandwidth h changes, the $RASE(\widehat{\beta}_0(\cdot))$ and $RASE(\widehat{\beta}_1(\cdot))$ varies a little, which indicates that the choice of three bandwidths will not quite affect the estimates of $\beta_0(t)$ and $\beta_1(t)$.

Table 4.3 present the biases, sample standard errors, estimated standard errors and the coverage probabilities related to γ in the case of mistreating T_{ij} as the measurement times since the actual time origin. Although both the standard errors of $\widehat{\gamma}$ increase compared to the third case with the same left censoring percentage, the biases are also small, the coverage probabilities are close to 0.95 and two types of standard errors are also close. This means even the time origin is mistreated, we can still get an unbiased estimator of γ since γ is time-independent.

Table 4.4 compare the RASE's in the two cases when the left censoring percentage of S_i is 50%. An obvious reduction of both RASE's is shown in the table.

Figure 4.1 shows the average estimates of $\beta(t) = (\beta_0(t), \beta_1(t))^T$ based on 500 simulations under four cases proposed above. Figure 4.1 (a), (b) and (c) are the plots of the average of the estimates based on the proposed method corresponding to 0%, 20% and 50% left censoring for S_i, and Figure 4.1 (d) corresponds to the fourth case. Figure 4.1 (a), (b) and (c) show that the estimated curves fit the true curve quite well. There is an obvious time shift for the covariate effect of X_i in Figure 4.1 (d).

Figure 4.2 shows both the standard errors of $\beta(t) = (\beta_0(t), \beta_1(t))^T$ based on 500 simulations under four cases proposed above. Figure 4.2 (a), (b) and (c) are the plots based on the proposed method corresponding to 0%, 20% and 50% left censoring for S_i, and Figure 4.2 (d) corresponds to the fourth case. In all four plots, the sample standard error curves are quite close to the estimated standard error curve. In the first three cases large variation near zero are typical for local linear approach near the boundaries; see Page 73 of Fan and Gijbels (1996). The case in Figure 4.2 (d) does not suffer from the large variation near zero since the new time zero is shifted from a time point that is of length S_i after actual time origin for ith subject, $i = 1, 2, \cdots, n$. In addition all subjects have responses measured at S_i.

Figure 4.3 shows the coverage probability of a pointwise 95% confidence interval for each component of $\beta(t) = (\beta_0(t), \beta_1(t))^T$ at each time point t based on 500 simulations under four cases proposed above. Figure 4.3 (a), (b) and (c) are the plots based on the proposed method corresponding to 0%, 20% and 50% left censoring for S_i, and Figure 4.3 (d) corresponds to the fourth case. The doted line in all four plots are the line when coverage probability is 95%. It is quite clear that all the coverage probabilities are close to 0.95.

Table 4.1: Summary statistics for the estimators $\widehat{\gamma}$ and $\widehat{\beta}(t)$ with no right censoring

c_L	n	h	Bias	SSE	ESE	CP	RASE($\widehat{\beta_0}(t)$)	RASE($\widehat{\beta_1}(t)$)
0%	200	0.3	−0.0090	0.1794	0.1780	0.958	0.0205	0.0479
		0.4	−0.0082	0.1794	0.1786	0.948	0.0172	0.0596
		0.5	−0.0078	0.1794	0.1790	0.954	0.0161	0.0858
	300	0.3	−0.0009	0.1386	0.1450	0.966	0.0182	0.0500
		0.4	0.0011	0.1385	0.1454	0.966	0.0163	0.0639
		0.5	0.0013	0.1384	0.1457	0.968	0.0160	0.0907
	500	0.3	−0.0083	0.1117	0.1134	0.950	0.0104	0.0323
		0.4	−0.0083	0.1116	0.1136	0.952	0.0064	0.0445
		0.5	−0.0081	0.1116	0.1137	0.950	0.0056	0.0724
20%	200	0.3	−0.0064	0.1809	0.1781	0.948	0.0279	0.0686
		0.4	−0.0064	0.1808	0.1788	0.946	0.0256	0.0758
		0.5	−0.0062	0.1810	0.1793	0.944	0.0241	0.0959
	300	0.3	0.0022	0.1426	0.1450	0.960	0.0314	0.0772
		0.4	0.0027	0.1427	0.1454	0.960	0.0310	0.0864
		0.5	0.0033	0.1426	0.1457	0.960	0.0289	0.1061
	500	0.3	−0.0059	0.1127	0.1135	0.942	0.0182	0.0704
		0.4	−0.0058	0.1127	0.1137	0.944	0.0154	0.0759
		0.5	−0.0057	0.1127	0.1139	0.944	0.0147	0.0914
50%	200	0.3	−0.0061	0.1821	0.1784	0.952	0.0905	0.2187
		0.4	−0.0055	0.1822	0.1795	0.952	0.0897	0.1960
		0.5	−0.0051	0.1822	0.1800	0.952	0.0547	0.1608
	300	0.3	0.0051	0.1418	0.1451	0.962	0.0725	0.1798
		0.4	0.0058	0.1417	0.1458	0.964	0.0672	0.1743
		0.5	0.0060	0.1417	0.1461	0.962	0.0585	0.1626
	500	0.3	−0.0050	0.1132	0.1138	0.942	0.0557	0.1824
		0.4	−0.0044	0.1133	0.1141	0.948	0.0485	0.1756
		0.5	−0.0041	0.1135	0.1143	0.942	0.0431	0.1615

Table 4.2: Summary statistics for the estimators $\widehat{\gamma}$ and $\widehat{\beta}(t)$ with 30% right censoring rate

c_L	n	h	Bias	SSE	ESE	CP	RASE($\widehat{\beta_0}(t)$)	RASE($\widehat{\beta_1}(t)$)
0%	200	0.3	-0.0131	0.1871	0.1836	0.946	0.0213	0.0479
		0.4	-0.0121	0.1873	0.1843	0.946	0.0179	0.0569
		0.5	-0.0113	0.1872	0.1848	0.950	0.0172	0.0823
	300	0.3	-0.0011	0.1436	0.1500	0.962	0.0243	0.0548
		0.4	-0.0009	0.1434	0.1504	0.968	0.0226	0.0667
		0.5	-0.0006	0.1432	0.1507	0.968	0.0223	0.0921
	500	0.3	-0.0092	0.1154	0.1173	0.948	0.0123	0.0334
		0.4	-0.0092	0.1152	0.1175	0.946	0.0076	0.0415
		0.5	-0.0089	0.1152	0.1177	0.944	0.0066	0.0677
20%	200	0.3	-0.0084	0.1874	0.1835	0.944	0.0330	0.0745
		0.4	-0.0085	0.1875	0.1844	0.950	0.0306	0.0784
		0.5	-0.0083	0.1879	0.1850	0.952	0.0290	0.0962
	300	0.3	0.0015	0.1468	0.1500	0.960	0.0376	0.0796
		0.4	0.0019	0.1469	0.1504	0.962	0.0381	0.0874
		0.5	0.0024	0.1470	0.1507	0.962	0.0362	0.1065
	500	0.3	-0.0066	0.1160	0.1174	0.942	0.0181	0.0773
		0.4	-0.0064	0.1158	0.1176	0.942	0.0148	0.0806
		0.5	-0.0063	0.1157	0.1178	0.942	0.0152	0.0924
50%	200	0.3	-0.0081	0.1897	0.1835	0.950	0.0921	0.2330
		0.4	-0.0077	0.1897	0.1847	0.952	0.0873	0.2065
		0.5	-0.0072	0.1898	0.1854	0.952	0.0565	0.1688
	300	0.3	0.0042	0.1467	0.1500	0.962	0.0773	0.1844
		0.4	0.0047	0.1468	0.1507	0.960	0.0736	0.1789
		0.5	0.0052	0.1467	0.1512	0.962	0.0653	0.1672
	500	0.3	-0.0057	0.1164	0.1175	0.942	0.0557	0.1935
		0.4	-0.0051	0.1163	0.1179	0.944	0.0491	0.1852
		0.5	-0.0049	0.1163	0.1182	0.942	0.0442	0.1683

Table 4.3: Summary statistics for the estimator $\widehat{\gamma}$ with misplaced time origin and 50% left censoring in the presence ($c_R = 30\%$) and absence ($c_R = 0\%$) of right censoring

c_R	n	h	Bias	SSE	ESE	CP
0%	200	0.3	−0.0016	0.2126	0.2119	0.946
		0.4	−0.0005	0.2122	0.2127	0.950
		0.5	0.0006	0.2121	0.2134	0.946
	300	0.3	0.0019	0.1746	0.1733	0.944
		0.4	0.0026	0.1746	0.1738	0.944
		0.5	0.0033	0.1745	0.1742	0.948
	500	0.3	−0.0066	0.1410	0.1349	0.932
		0.4	−0.0058	0.1407	0.1352	0.932
		0.5	−0.0052	0.1404	0.1354	0.932
30%	200	0.3	0.0003	0.2251	0.2262	0.946
		0.4	0.0014	0.2251	0.2272	0.946
		0.5	0.0027	0.2250	0.2281	0.946
	300	0.3	0.0019	0.1853	0.1865	0.938
		0.4	0.0029	0.1848	0.1871	0.940
		0.5	0.0040	0.1845	0.1876	0.946
	500	0.3	−0.0106	0.1487	0.1449	0.936
		0.4	−0.0096	0.1486	0.1452	0.936
		0.5	−0.0086	0.1480	0.1455	0.942

Table 4.4: Summary statistics for the estimator $\widehat{\beta}(t)$ for misplaced time origin and 50% left censoring in the presence ($c_R = 30\%$) and absence ($c_R = 0\%$) of right censoring

			RASE($\widehat{\beta}_0(t)$)		RASE($\widehat{\beta}_1(t)$)	
c_R	n	h	Our method	Misplaced time origin	Our method	Misplaced time origin
0%	200	0.3	0.0905	0.3959	0.2187	1.4308
		0.4	0.0897	0.3979	0.1960	1.4260
		0.5	0.0547	0.3991	0.1608	1.4229
	300	0.3	0.0725	0.3860	0.1798	1.4345
		0.4	0.0672	0.3870	0.1743	1.4309
		0.5	0.0585	0.3871	0.1626	1.4284
	500	0.3	0.0557	0.4050	0.1824	1.4057
		0.4	0.0544	0.4063	0.1711	1.4024
		0.5	0.0431	0.4070	0.1615	1.3995
30%	200	0.3	0.0921	0.4009	0.2330	1.4222
		0.4	0.0873	0.4007	0.2065	1.4099
		0.5	0.0565	0.4044	0.1688	1.4035
	300	0.3	0.0773	0.3799	0.1844	1.4373
		0.4	0.0736	0.3805	0.1789	1.4329
		0.5	0.0653	0.3812	0.1672	1.4305
	500	0.3	0.0557	0.4061	0.1935	1.3985
		0.4	0.0491	0.4071	0.1852	1.3940
		0.5	0.0442	0.4077	0.1683	1.3917

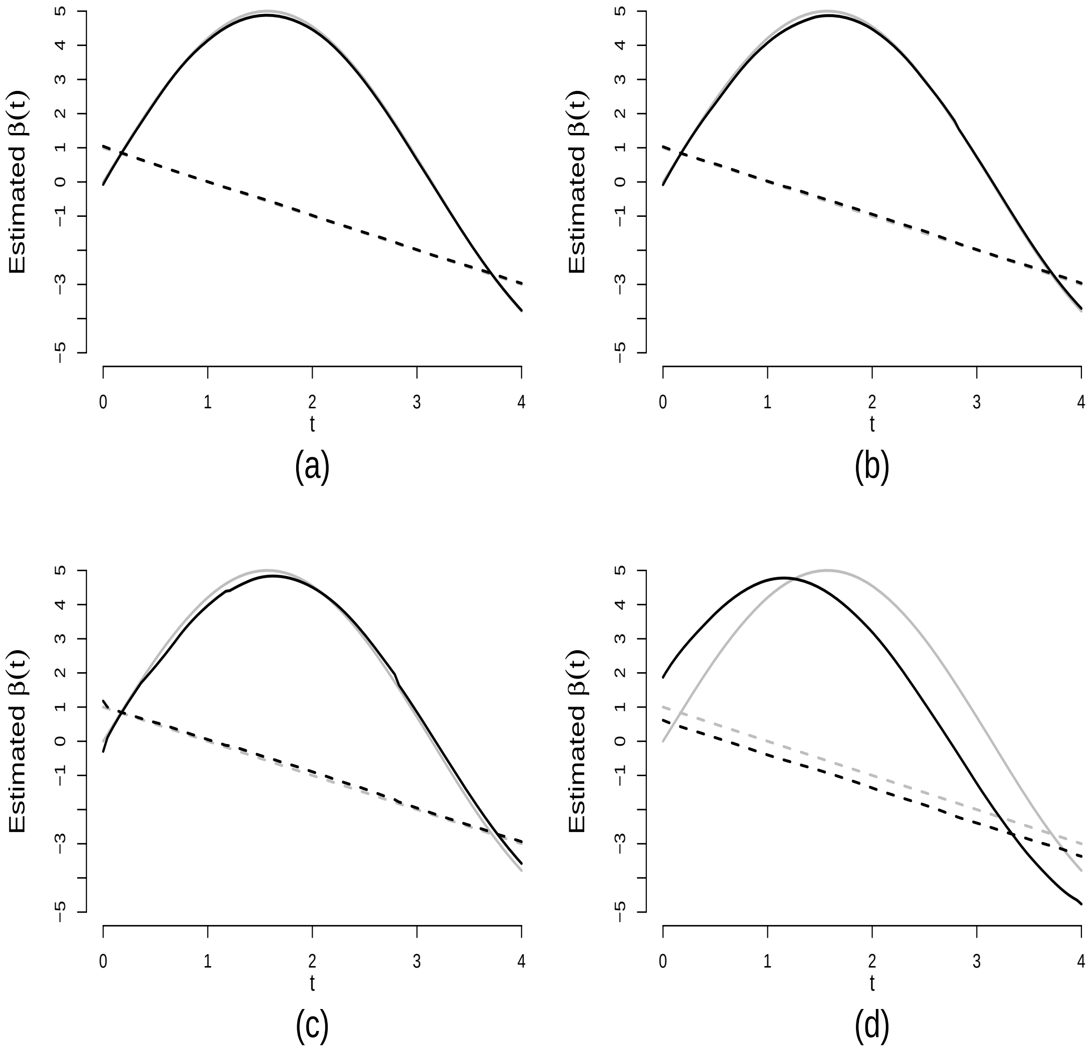


Figure 4.1: The averages of the estimator $\beta(t) = (\beta_0(t), \beta_1(t))^T$ for $n = 300$, $h = 0.4$ and 30% right censoring rate. The solid lines are for $\beta_1(t)$ and the dashed lines are for $\beta_0(t)$. The grey lines are the true curves. Figures (a), (b) and (c) shows the averages in the cases of 0%, 20% and 50% left censoring rate of S_i respectively. Figure (d) shows the results in the case of misplaced time origin by ignoring S_i.

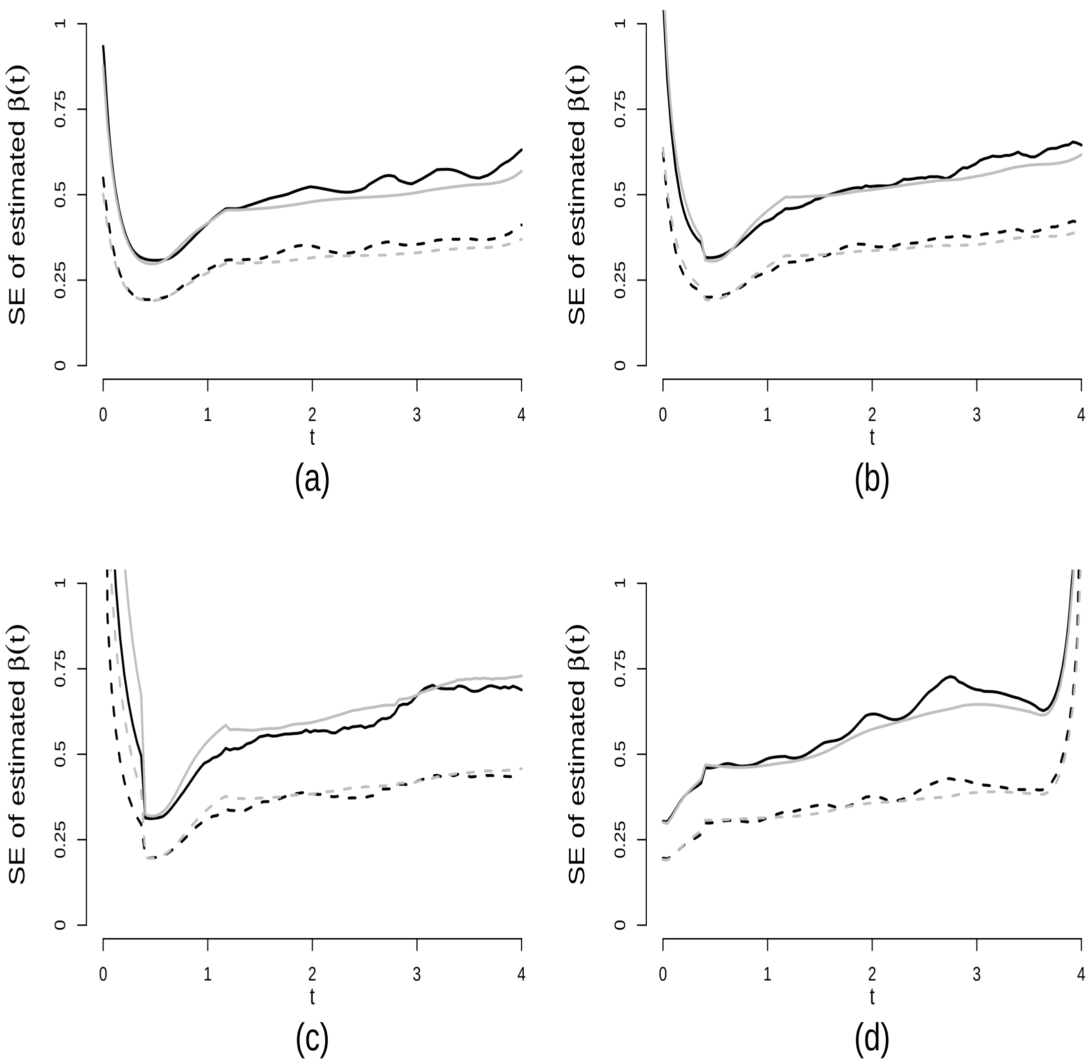


Figure 4.2: The sample and estimated standard errors of the estimator $\beta(t) = (\beta_0(t), \beta_1(t))^T$ for $n = 300$, $h = 0.4$ and 30% right censoring rate. The solid lines are for $\beta_1(t)$ and the dashed lines are for $\beta_0(t)$. The grey lines are the estimated standard error and the black ones are the sample standard error. Figures (a), (b) and (c) shows the results in the cases of 0%, 20% and 50% left censoring rate of S_i respectively. Figure (d) shows the results in the case of misplaced time origin by ignoring S_i.

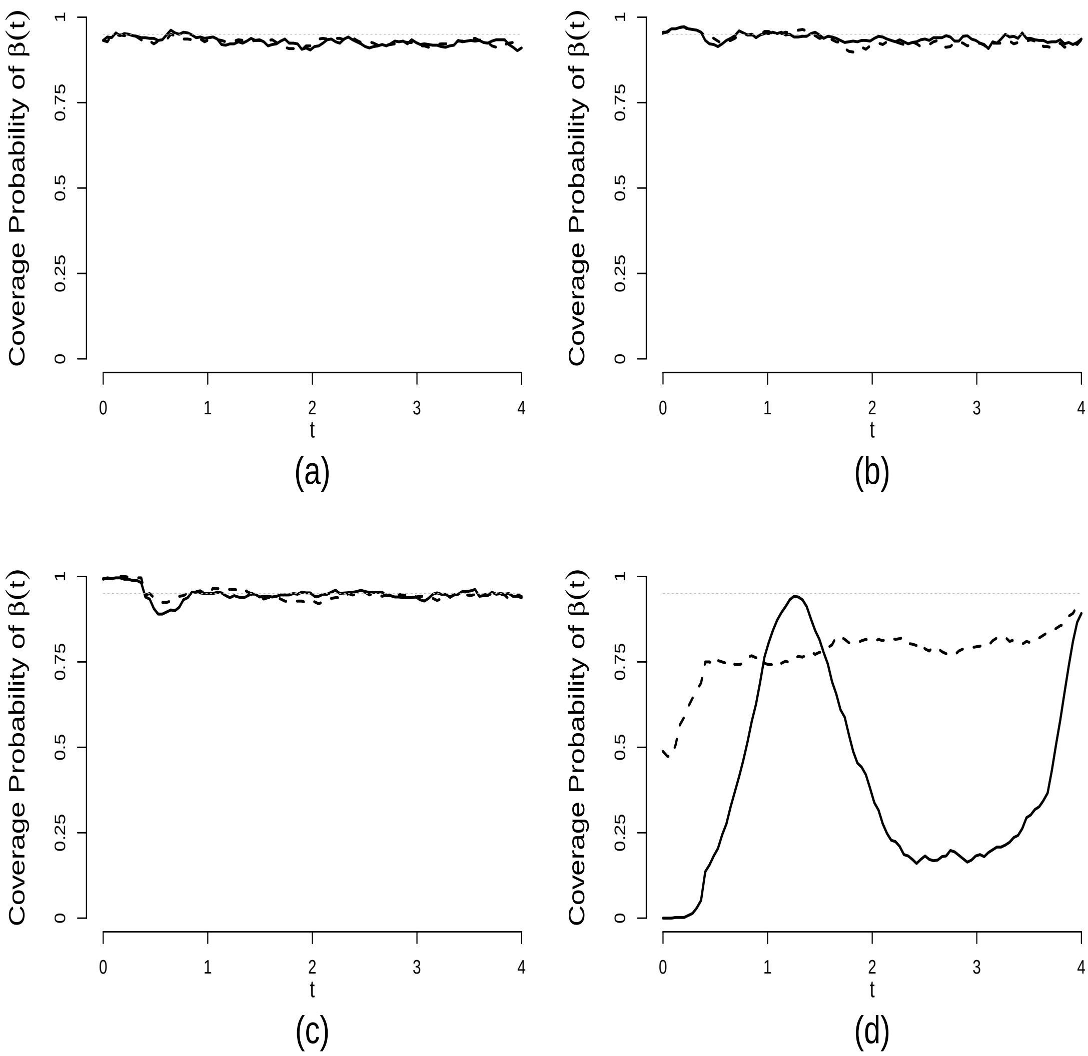


Figure 4.3: The coverage probabilities of 95% pointwise confidence intervals of $\beta(t) = (\beta_0(t), \beta_1(t))^T$ for $n = 300$, $h = 0.4$ and 30% right censoring rate. The solid lines are for $\beta_1(t)$ and the dashed lines are for $\beta_0(t)$. Figures (a), (b) and (c) shows the averages in the cases of 0%, 20% and 50% left censoring rate of S_i respectively. Figure (d) shows the results in the case of misplaced time origin by ignoring S_i.

CHAPTER 5: REAL DATA APPLICATION

In this chapter a real data from the STEP study (cf., Buchbinder et al., 2008; Fitzgerald et al., 2011) is analyzed by applying the methods discussed in previous chapters. The step study was a multicenter, double-blind, randomized, placebo-controlled, phase II test-of-concept study to determine whether the MRKAd5 HIV-1 gag/pol/nef vaccine, which elicits T cell immunity, is capable to result in controlling the replication of the Human immunodeficiency virus among the participants who got HIV-infected after vaccination. This study opened in December 2004 and was conducted at 34 sites in North America, the Caribbean, South America, and Australia. Three thousand HIV-1 negative participants aged from 18 to 45 who were at high risk of HIV-infection were enrolled and randomly assigned to receive vaccine or placebo in ratio 1:1, stratified by sex, study site and adenovirus type 5 (Ad5) antibody titer at baseline. Some of the participants were fully adherent to vaccinations while others not.

The analysis in this chapter includes a subset of the 3000 participants which involves all 174 MITT cases as of September 22, 2009. MITT cases stand for modified intention-to-treat subjects who became HIV infected during the trial. The modified inention to treat refers to all randomized subjects, excluding the few that were found to be HIV infected at entry. It is recommended to study males only, for the entire analysis to avoid the effect of sex since there are only 15 females that are $< 10\%$ of the sample. There were 159 HIV-infected males. Each participant had the records of the first positive diagnosis (the dates of their first positive Elisa confirmed by Western Blot or RNA, illustrated as D_i's in Figure 1.1), the dates of their first evidence of infection (determined by the dates of the first positive RNA (PCR) test), and the estimated dates of infection. The estimated dates of infection is considered as the midpoint between last RNA negative visit date (L_i's in Figure 1.1) and the date of first evidence of infection. The last RNA negative visit date can be computed by the estimated date of infection and the dates of their first evidence of infection. As such, we calculate V_i by $V_i = D_i - L_i = D_i - 2\times$ estimated infection dates + the date of first evidence of infection. The indicator of whether the actual acquisition of ith subject is observed or not is denoted by R_i; $R_i = 1$ if the actual HIV acquisition date can be determined by using the RNA test, and in this case the duration between actual HIV acquisition and the first positive diagnosis date $S_i = V_i$; otherwise $R_i = 0$ and $S_i < V_i$.

After the participant was infected, there were 18 scheduled post-infection visits per subject at weeks 0, 1, 2, 8, 12, 26, and every 26 weeks thereafter through week 338. However, the actual times and dates of visits may vary due to each individual. During jth visit, the ith subject received tests to have the measurements of HIV virus load and CD4 cell counts before the subject started the antiretroviral therapy (ART) or was censored. And the time from the first positive Elisa to the jth visit for ith subject is T_{ij} in the above chapters. The time between the first positive Elisa and ART initiation or censoring for subject i is the right censoring time C_i. In the analysis time is measured in years. Let Y be the common logarithm of HIV virus load, X_1 be the square root of CD4 counts, X_2 be the treatment indicator ($X_2 = 1$ if the subject received vaccine and 0 if receiving placebo), Z_1 be the site indicator ($Z_1 = 1$ if North America or Australia and 0 otherwise), Z_2 be the natural logarithm of Ad5 and Z_3 be the pre-protocol indicator ($Z_3 = 1$ if the subject was fully adherent to vaccinations and 0 otherwise). Our main interest is to see the effect of vaccine on the HIV virus load response.

In the data 159 males made a total of 791 pre-ART visits. Among them there are 156 missing in CD4 cell counts and 5 missing in HIV virus load. Since there are no missing in CD4 and virus load at the same time, we could use a simple imputation model to create a complete data set. At each time point separately, we use a linear regression model linking $\log_{10}$(viral load) to square root of CD4 count (for those with data on both), and use the viral load value for those with missing data to fill in the missing CD4 cell count or predict missing virus load data by CD4 values. However, at three time points there are no complete data for conducting the linear regression model fitting; at two other points there are only one complete data which is unable to complete the linear model fitting; at another time point one predicted value of virus load is relatively far beyond the range of other values of virus load and may affect the analysis results. Therefore, we delete these six visits to get the complete data for the entire analysis.

Now in this complete data set there are 159 subjects with 785 visits. 97 Of all the participants were in the vaccine group while 62 received the placebo. 122 subjects participate in the study in North America or Australia and the rest are residents in the other sites mentioned at the beginning of this chapter. The left censoring rate of S_i is 70.44% and the right censoring rate of T_{ij} is 69.81%. Figure 5.1 to Figure 5.3 are further exploration of the data. It is easy to figure out that there are few data after time point 2.5. Therefore, we will choose $t_1 = 0$ and $t_2 = 2.5$ to estimate γ, and also plot the estimators of $\beta(t)$'s for the time points in the interval [0,2.5]. Finally, Figure 5.4 shows the Kaplan Meier estimator of the distribution of S_i. Note that the smallest observed S_i is 0.14. Before that time we do not have enough information to get the estimator of the distribution. However, since time is always nonnegative, the probability of S_i reduce to 0 at $S_i = 0$.

After preliminary exploration of the data, we propose the following model for virus load response of the ith subject in this study:

$$Y_i(t) = \beta_0(t) + \beta_1(t)X_{1i}(t) + \beta_2(t)X_{2i} + \gamma_1 Z_{1i} + \gamma_2 Z_{2i} + \gamma_3 Z_{3i} + \epsilon_i(t). \qquad (5.1)$$

By the study of simulation and several tries of different bandwidths, a possible reasonable choice of the bandwidth for this data set is 0.5. And we still consider the unit weight for the analysis. The estimates of γ_1, γ_2 and γ_3 are 0.0302, -0.1467 and 0.1956, with the standard deviations 0.0389, 0.1492 and 0.1540, respectively. The p-values for testing $H_0 : \gamma_1 = 0$, $H_0 : \gamma_2 = 0$ and $H_0 : \gamma_3 = 0$ are equal to 0.4375, 0.3255 and 0.2042, respectively, which indicates that there are no significant effects of baseline Ad5 titer, study sites or the pre-protocol on the HIV viral load level at 5% significance level. The estimates of time-dependent effects and their 95% pointwise confidence intervals are shown in Figure 5.5. From the graph although the effects of vaccine or CD4 cell count on the HIV viral load level are not statistically significant, both of them have negative trend of HIV viral load. Further hypothesis test study will be done in the future. Finally Figure 5.6 shows the scatter plot of the residuals of subjects with $R_i = 1$ from fitting the model (5.1).

From Figure 5.5, it is reasonable to suspect that there is constant effect on both treatment and CD4 cell counts. More rigorously we could conduct hypothesis tests for the constant effect. This work will be done in the future. So let us consider the new fitting model

$$Y_i(t) = \beta_0(t) + \gamma_1 X_{1i}(t) + \gamma_2 X_{2i} + \gamma_3 Z_{1i} + \gamma_4 Z_{2i} + \gamma_5 Z_{3i} + \epsilon_i(t). \tag{5.2}$$

We remain using 0.5 as the bandwidth and the unit weight. The estimates of [γ_1, γ_2, γ_3, γ_4, γ_5] are [-0.0624, -0.0568, 0.0227, -0.0937, 0.1757], with the standard deviations 0.0114, 0.1237, 0.0380, 0.1521 and 0.1435, respectively. The p-values for testing $H_0 : \gamma_i = 0$, $i = 1, 2, \cdots, 5$ are equal to <0.0001, 0.6463, 0.5496, 0.5379 and 0.2210, respectively, which indicates that square root of Cd4 cell counts has significantly negative effects on $\log_{10}$-transformed virus load while there are no significant effects of the treatment, baseline Ad5 titer, study sites or the pre-protocol on the HIV viral load level at 5% significance level. The estimates of time-dependent intercept and its 95% pointwise confidence intervals are shown in Figure 5.7. Figure 5.8 shows the scatter plot of the residuals of subjects with $R_i = 1$ from fitting the model (5.2).

Here in both fitting models there are five independent variables. So we can conduct model selection in the future.

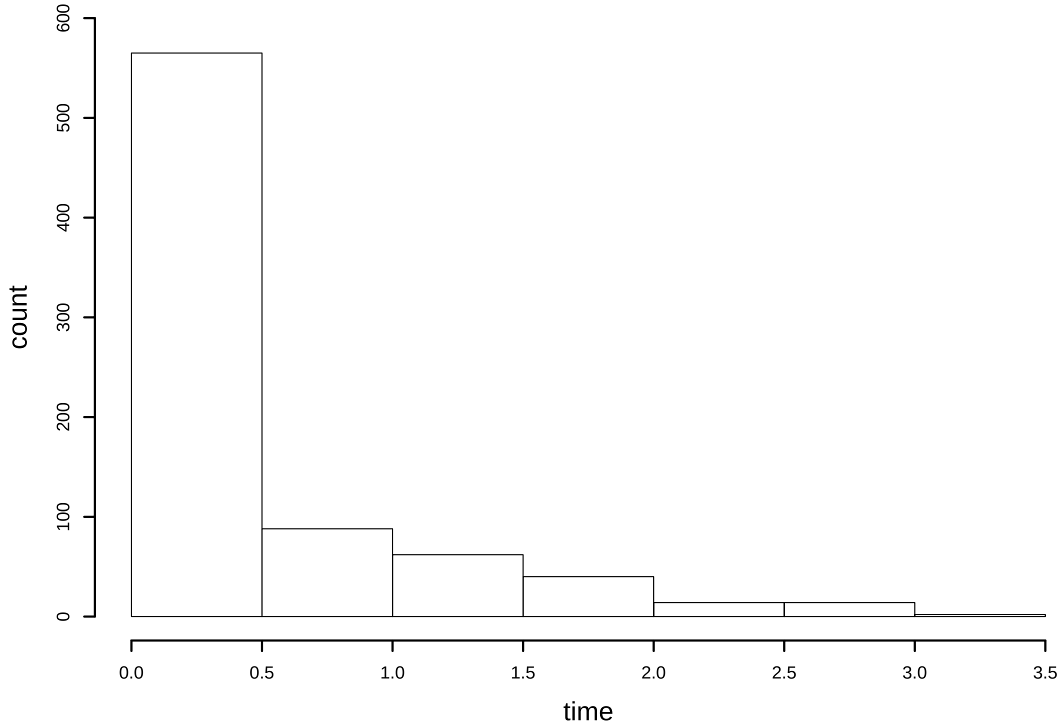
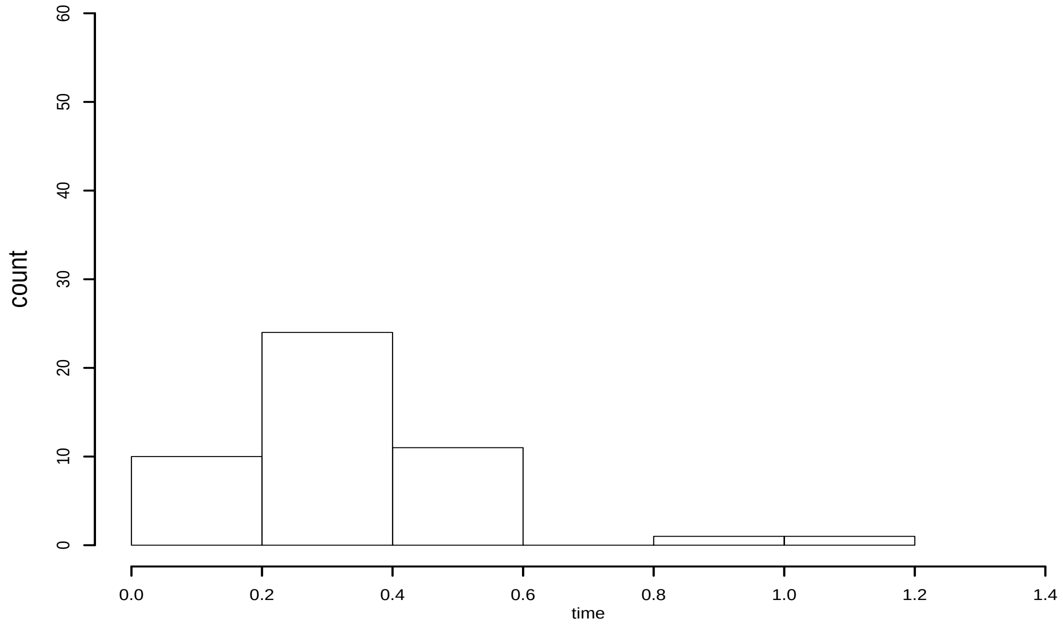
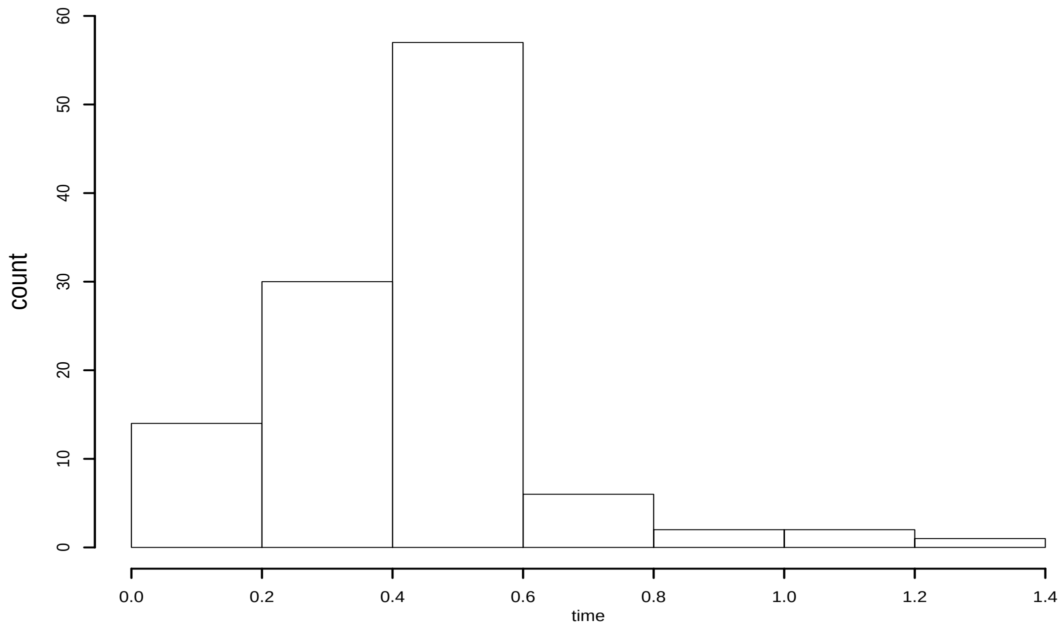


Figure 5.1: Histogram of times (T_{ij}) from the first positive Elisa confirmed by Western Blot or RNA to subsquent visits.



(a)



(b)

Figure 5.2: Histograms of times (V_i) from actual HIV acquisition to the first positive Elisa confirmed by Western Blot or RNA. Figure (a) shows the histogram of observed V_i's ($R_i = 1$) while Figure (b) shows the counts of censored V_i's ($R_i = 0$).

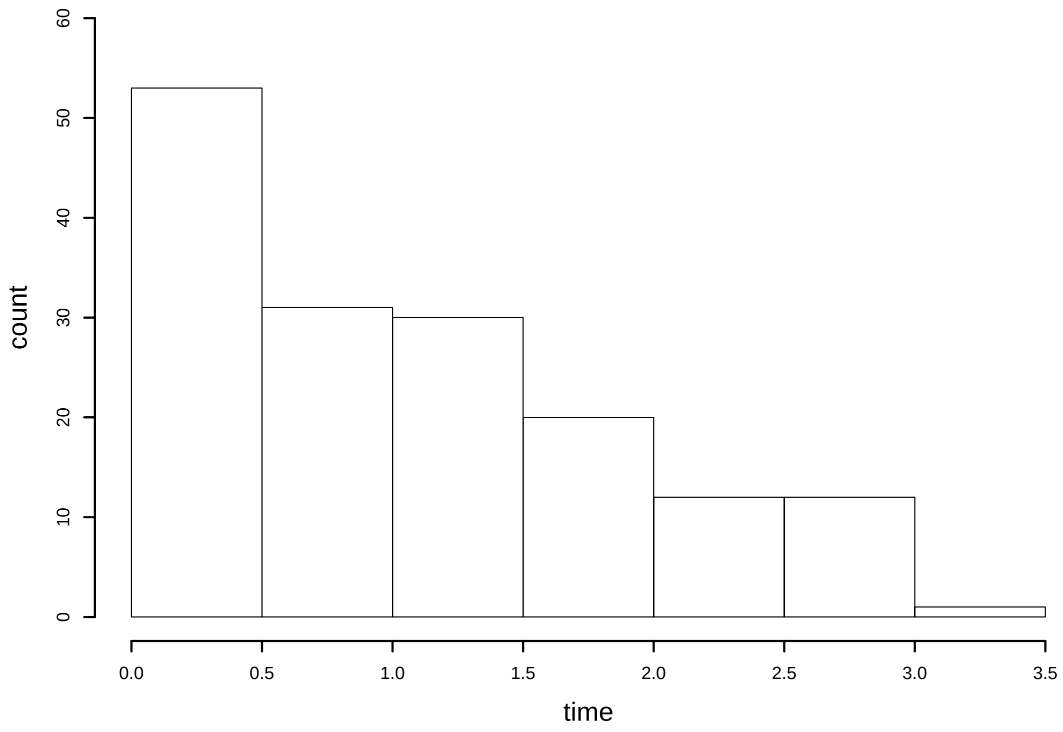


Figure 5.3: Histograms of times (C_i) from the first positive Elisa confirmed by Western Blot or RNA to ART initiation or censoring.

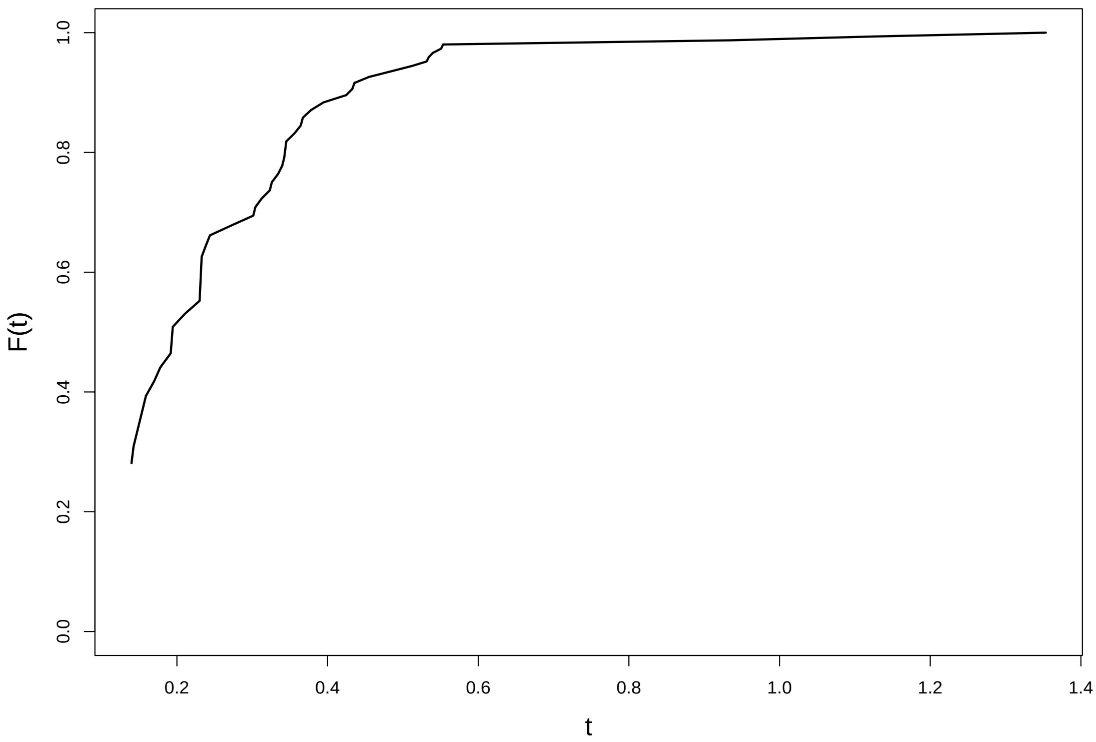


Figure 5.4: The Kaplan Meier estimator of the distribution function of the time from actual HIV acquisition to the first positive Elisa confirmed by Western Blot or RNA.

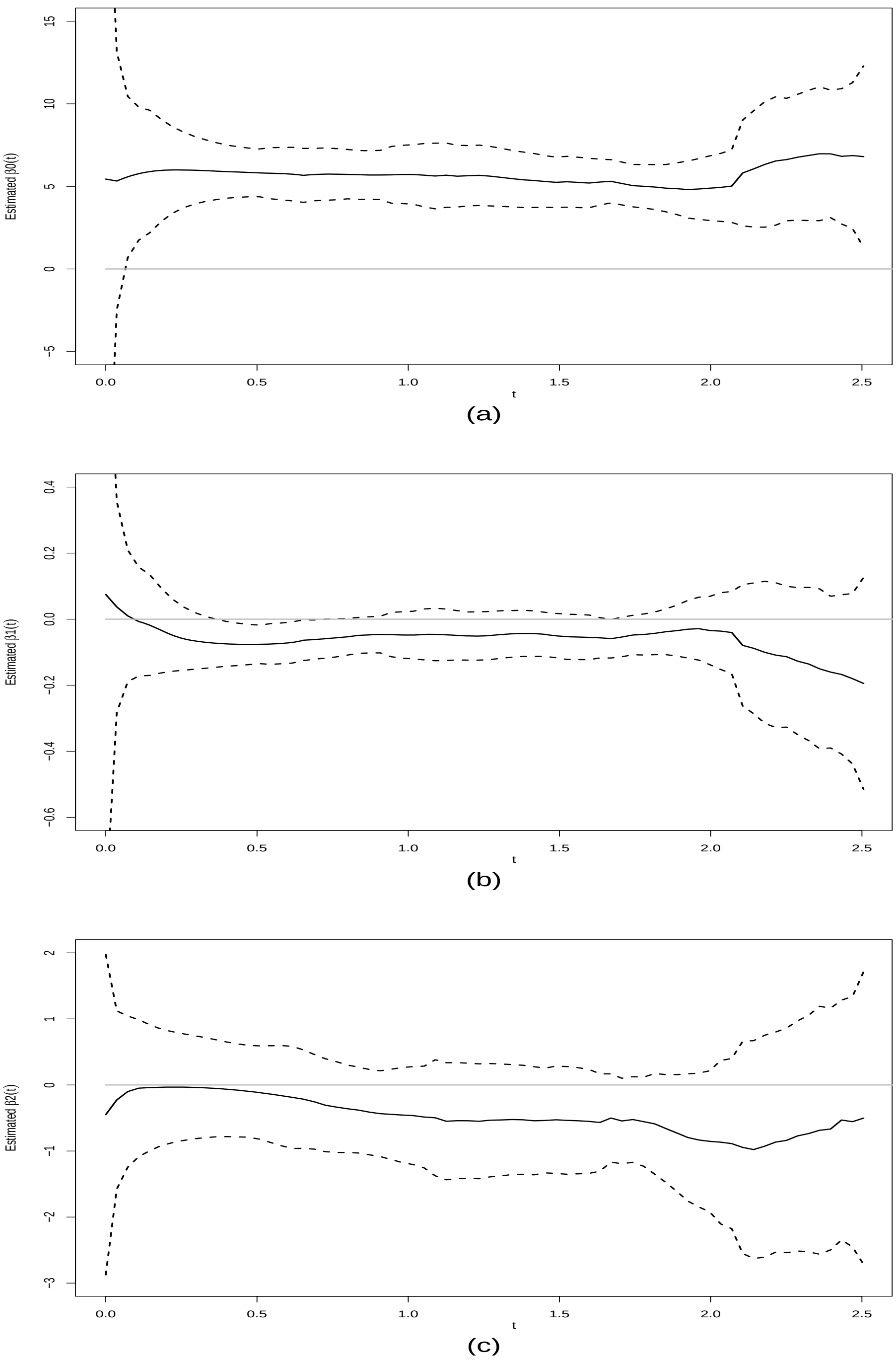


Figure 5.5: Estimation of $\beta(t) = (\beta_0(t), \beta_1(t), \beta_2(t))^T$ based on the data from STEP study with MITT cases. Figure (a) shows the estimated intercept, $\beta_0(t)$ and its 95% pointwise confidence interval. Figure (b) shows the estimated effect of the square root of CD4 effect, $\beta_1(t)$ and its 95% pointwise confidence interval. Figure (c) shows the estimated treatment effect, $\beta_2(t)$ and its 95% pointwise confidence interval. The solid curves are the estimated curves and the dashed curves are the confidence intervals.

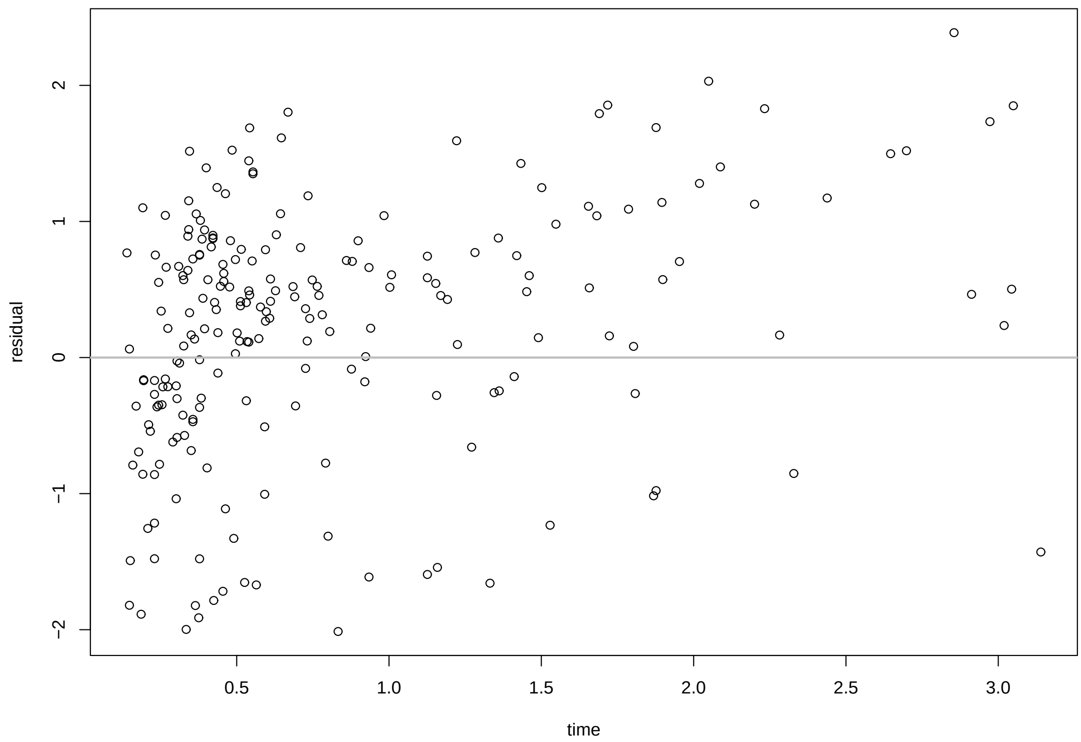


Figure 5.6: The scatter plot of residuals of the subjects with $R_i = 1$.

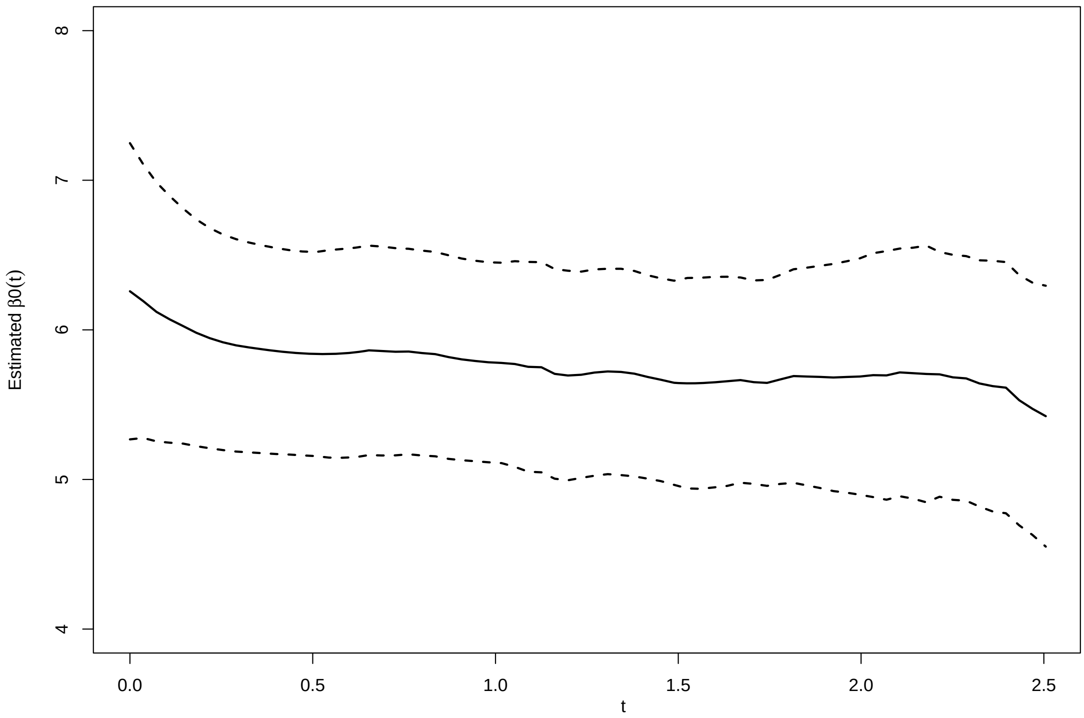


Figure 5.7: The estimated intercept, $\beta_0(t)$ and its 95% pointwise confidence interval under Model 5.2, based on the data from STEP study with MITT cases. The solid curves are the estimated curves and the dashed curves are the confidence intervals.

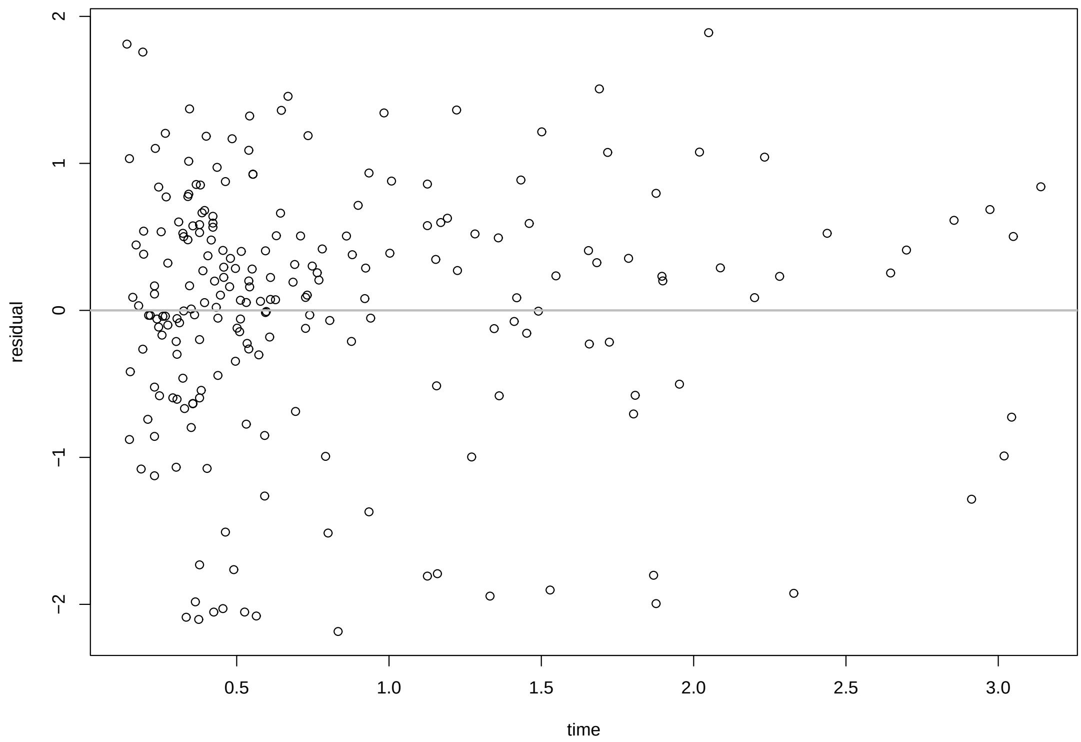


Figure 5.8: The scatter plot of residuals of the subjects with $R_i = 1$ under Model 5.2.

CHAPTER 6: FUTURE WORKS

As mentioned in Chapter 5.1, it is more rigorous to test whether there are constant effects of $X_i(t)$ before we fitting Model (5.2). This test is based on the asymptotic properties of estimator of integrated time-dependent effects, i.e. $\widehat{\mathcal{B}}(t) = \int_0^t \widehat{\beta}(s)ds$. These asymptotic results can be obtained by using our lemmas in Appendix A.2. After that, besides testing constant effect of $X_i(t)$, we can also test whether there is no effect of $X_i(t)$.

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APPENDIX A: PROOF OF LEMMA AND THEOREM

In this chapter, we provide the proofs of Theorem 3.1 to 3.4. Six technique lemmas are presented and proved first in Section A.2. Lemma A.2.1 to A.2.6 are to be used in the proofs of Theorem 3.1 to 3.4 in Section A.3.

A.1 Preliminaries

For simplicity we derive the asymptotic results under the assumption that S_i and $\mathcal{D}_i$ are independent. Preparing for future application in this section, we first derive the martingale decomposition of the Kaplan-Meier estimator of the survival function for the left censored data.

In general, we have the i.i.d. data structure of the left censored data as follows,

$$\{T_i = max(S_i, C_i), \delta_i = I(S_i \geq C_i)\},$$

where S_i is the failure time censored by C_i, T_i is observed time and δ_i is the indicator of non-censorship for ith subject. Suppose L be a large enough number so that all $S_i < L$. Then

$$\{L - T_i = min(L - S_i, L - C_i), \delta_i = I(L - S_i \leq L - C_i)\}$$

is the corresponding right censored data structure. Let $S(t) = P(S_i > t)$ and $S^S(t) = P(L - S_i > t)$ be the survival functions of the failure time for the left and right censored data respectively. And $\widehat{S}(t)$, $\widehat{S}^S(t)$ are the Kaplan-Meyer estimators of the survival functions respectively. Now define the counting process $N_i^S(t) = I(L - T_i \leq t, \delta_i = 1)$. By the Doob-Meyer decomposition, there is a compensator $\int_0^t Y_i^S(s) d\Lambda^S(s)$ and a martingale $M_i^S(t)$ so that $N_i^S(t) = \int_0^t Y_i^S(s) d\Lambda^S(s) + M_i^S(t)$. Here $Y_i^S(t) = I(L - T_i \geq t)$ is the at risk indicator and $\Lambda^S(t)$ is the cumulative hazard function. Let $N^S(t) = \sum_{i=1}^n N_i^S(t)$, $M^S(t) = \sum_{i=1}^n M_i^S(t)$ and $Y^S(t) = \sum_{i=1}^n Y_i^S(t) = \sum_{i=1}^n I(T_i \leq L - t)$. Assume that $Y^S(t)/n \xrightarrow{P} y^S(t)$. Hence according to Equation (2.11) in Chapter 3 on Page 98 of Fleming & Harrington (1991), we have the decomposition

$$n^{1/2}(\widehat{S}^S(t) - S^S(t)) = -n^{1/2}S^S(t)\int_0^t \frac{\widehat{S}^S(s-)}{S^S(s)}\frac{I(Y^S(s)>0)}{Y^S(s)}dM^S(s) + o_p(1).$$

Since

$$S(t) = P(S_i > t) = P(L - S_i < L - t) = 1 - P(L - S_i \geq L - t) = 1 - S^S((L-t)-),$$

then for the left censored data

$$\begin{aligned}
& n^{1/2}(\widehat{S}(t) - S(t)) \\
= & -n^{1/2}[\widehat{S}^S((L-t)-) - S^S((L-t)-)] \\
= & n^{1/2}S^S((L-t)-)\int_0^{(L-t)-} \frac{\widehat{S}^S(s-)}{S^S(s)}\frac{I(Y^S(s)>0)}{Y^S(s)}dM^S(s) + o_p(1) \\
= & n^{-1/2}(1-S(t))\int_0^{(L-t)-} \frac{1-\widehat{S}(L-s)}{1-S((L-s)-)}\frac{I(Y^S(s)>0)}{Y^S(s)/n}dM^S(s) + o_p(1) \\
= & n^{-1/2}(1-S(t))\int_0^{(L-t)-} \frac{1}{y^S(s)}dM^S(s) + o_p(1). \qquad (A.1)
\end{aligned}$$

Under Conditions (II), $n^{1/2}(\widehat{S}(t) - S(t))$ converges weakly on $[0, \infty]$ by Ying (1989).

Now let us define the following notations for the future use.

$$X_{zi}^I(t) = \int_0^t [R_i Z_i(u) X_i^T(u) dN_i^c(u) - E(R_i \xi_i(u)\alpha_i(u) Z_i(u) X_i^T(u))du], \qquad (A.2)$$

$$\begin{aligned}
X_{zi}^{II}(t) = & \int_0^\infty \int_0^L \int_{t_1}^t E\Big\{(1-R_i)Z_i(u)X_i^T(u)\alpha_i^*(u-s)\frac{I(x \leq (L-V_i)-)}{F_s(V_i)}\Big\} \\
& du dF_s(s)\frac{dM_i^S(x)}{y^S(x)} \\
& - \int_0^{L-}\int_0^{(L-x)-}\int_{t_1}^t E\Big\{(1-R_i)\frac{Z_i(u)X_i^T(u)\alpha_i^*(u-s)}{F_s(V_i)}\Big\}du\, dF_s(s)\frac{dM_i^S(x)}{y^S(x)} \\
& + \int_0^L \int_{t_1}^t E\Big\{(1-R_i)\frac{Z_i(u)X_i^T(u)\alpha_i^*(u-s)}{F_s(V_i)}\Big\}F_s(s)du\frac{dM_i^S((L-s)-)}{y^S((L-s)-)}, \qquad (A.3)
\end{aligned}$$

$$\begin{aligned}
X_{zi}^{III}(t) = & \int_0^t (E_s\{(1-R_i)Z_i(u)X_i^T(u)dN_i^c(u) \mid \mathcal{D}_i, R_i = 0\} \\
& -E\{(1-R_i)\xi_i(u)\alpha_i(u)Z_i(u)X_i^T(u)\}du), \qquad (A.4)
\end{aligned}$$

and

$$X_{zn}^{I}(t)=n^{-1/2}\sum_{i=1}^{n}X_{zi}^{I}(t), X_{zn}^{II}(t)=n^{-1/2}\sum_{i=1}^{n}X_{zi}^{II}(t), X_{zn}^{III}(t)=n^{-1/2}\sum_{i=1}^{n}X_{zi}^{III}(t).$$

Similarly, we define $X_{yi}^{I}(t)$, $X_{yi}^{II}(t)$, $X_{yi}^{III}(t)$, $X_{yn}^{I}(t)$, $X_{yn}^{II}(t)$, $X_{yn}^{III}(t)$ by replacing $Z_i(\cdot)$ with $Y_i(\cdot)$ respectively. $X_{xi}^{I}(t)$, $X_{xi}^{II}(t)$, $X_{xi}^{III}(t)$, $X_{xn}^{I}(t)$, $X_{xn}^{II}(t)$, $X_{xn}^{III}(t)$ are similarly defined by replacing $Z_i(\cdot)$ with $X_i(\cdot)$ respectively.

A.2 Some Lemmas

Lemma A.2.1: Let $g(t,x,z,y)$ be a continuous function of (t,x,z,y) and $g_i(t) = g(t, X_i(t), Z_i(t), Y_i(t))$. Then under Conditions (I) and (II),

$$n^{-1}\sum_{i=1}^{n}(1-R_i)\widehat{E}_s\Big\{\int_{t_1}^{t} g_i(u)dN_i^c(u) \mid \mathcal{D}_i, R_i=0\Big\} \xrightarrow{P} E\Big\{(1-R_i)\int_{t_1}^{t} g_i(u)dN_i^c(u)\Big\}$$

uniformly in $t \in [t_1,t_2] \subset (0,\tau)$ as $n\to\infty$.

Proof. Let $\xi_i^*(s,v) = I(t_1 \le s+v \le t)I(s < V_i)I(C_i \ge v)$. Since S_i is independent of $\mathcal{D}_i$, under conditions (II) and by (2.4),

$$\begin{aligned}
& n^{-1}\sum_{i=1}^{n}(1-R_i)\widehat{E}_s\Big\{\int_{t_1}^{t} g_i(u)dN_i^c(u) \mid \mathcal{D}_i, R_i=0\Big\} \\
= & n^{-1}\sum_{i=1}^{n}(1-R_i)\int_{s_0}^{L}\sum_{j=1}^{n_i} g_i(s+T_{ij})\xi_i^*(s,T_{ij})\frac{d\widehat{F}_s(s)}{\widehat{F}_s(V_i)} \\
= & n^{-1}\sum_{i=1}^{n}(1-R_i)\int_{s_0}^{L}\sum_{j=1}^{n_i} g_i(s+T_{ij})\xi_i^*(s,T_{ij})\frac{dF_s(s)}{F_s(V_i)} \\
& +n^{-1}\sum_{i=1}^{n}(1-R_i)\int_{s_0}^{L}\sum_{j=1}^{n_i} g_i(s+T_{ij})\xi_i^*(s,T_{ij})\Big(\frac{dF_s(s)}{\widehat{F}_s(V_i)}-\frac{dF_s(s)}{F_s(V_i)}\Big) \\
& +n^{-1}\sum_{i=1}^{n}(1-R_i)\int_{s_0}^{L}\sum_{j=1}^{n_i} g_i(s+T_{ij})\xi_i^*(s,T_{ij})\frac{d\widehat{F}_s(s)-dF_s(s)}{\widehat{F}_s(V_i)}
\end{aligned} \quad (A.5)$$

Since $\widehat{F}_s(s)$ is the Kaplan-Meier estimator, under Conditions (II), by Theorem 3.1 of Sun (1997) and relative work in Ying (1989), we have $\widehat{F}_s(s) \xrightarrow{P} F_s(s)$ uniformly in $s \in [s_0, L]$. Then $\widehat{F}_s(V_i) \xrightarrow{P} F_s(V_i)$ since $P(V_i > s_0) = 1$. By the continuous mapping theorem, $1/\widehat{F}_s(V_i) \xrightarrow{P} 1/F_s(V_i)$. Under Conditions (I) the second term in (A.5)

$$\begin{aligned}
& n^{-1}\sum_{i=1}^{n}(1-R_i)\int_{s_0}^{L}\sum_{j=1}^{n_i} g_i(s+T_{ij})\xi_i^*(s,T_{ij})\left(\frac{1}{\widehat{F}_s(V_i)}-\frac{1}{F_s(V_i)}\right)dF_s(s) \\
= \;& n^{-1}\sum_{i=1}^{n}\left(\frac{1}{\widehat{F}_s(V_i)}-\frac{1}{F_s(V_i)}\right)(1-R_i)\int_{s_0}^{L}\sum_{j=1}^{n_i} g_i(s+T_{ij})\xi_i^*(s,T_{ij})dF_s(s)
\end{aligned}$$

converges to zero in probability. Note that $N_i(t)=\sum_{j=1}^{n_i} I(T_{ij}\le t)$, the third term in (A.5) is equal to

$$\begin{aligned}
& n^{-1}\sum_{i=1}^{n}(1-R_i)\int_{s_0}^{L}\sum_{j=1}^{n_i} g_i(s+T_{ij})\xi_i^*(s,T_{ij})\frac{d\widehat{F}_s(s)-dF_s(s)}{F_s(V_i)}+o_p(1) \\
= \;& n^{-1}\sum_{i=1}^{n}(1-R_i)\int_{s_0}^{L}\left(\int_{-s}^{\tau-s} g_i(s+v)\xi_i^*(s,v)dN_i(v)\right)\frac{d(\widehat{F}_s(s)-F_s(s))}{F_s(V_i)} \\
& +o_p(1) \\
= \;& \int_{s_0}^{L}\left[n^{-1}\sum_{i=1}^{n}(1-R_i)\int_{-s}^{\tau-s} g_i(s+v)\xi_i^*(s,v)dN_i(v)\frac{1}{F_s(V_i)}\right]d(\widehat{F}_s(s)-F_s(s)) \\
& +o_p(1)
\end{aligned}$$

Let

$$H_n(s)=n^{-1}\sum_{i=1}^{n}(1-R_i)\int_{-s}^{\tau-s} g_i(s+v)\xi_i^*(s,v)dN_i(v)\frac{1}{F_s(V_i)}.$$

So the absolute value of the third term in (A.5) equals

$$\begin{aligned}
& \left|\int_{s_0}^{L} H_n(s)d(\widehat{F}_s(s)-F_s(s))\right| \\
= \;& \left|H_n(L)(\widehat{F}_s(L)-F_s(L))-H_n(s_0)(\widehat{F}_s(s_0)-F_s(s_0))-\int_{s_0}^{L}(\widehat{F}_s(s)-F_s(s))dH_n(s)\right| \\
\le \;& |H_n(L)(\widehat{F}_s(L)-F_s(L))|+|H_n(s_0)(\widehat{F}_s(s_0)-F_s(s_0))|+\left|\int_{s_0}^{L}(\widehat{F}_s(s)-F_s(s))dH_n(s)\right| \\
\le \;& |H_n(L)(\widehat{F}_s(L)-F_s(L))|+|H_n(s_0)(\widehat{F}_s(s_0)-F_s(s_0))| \\
& +\sup_{s\in[s_0,L]}|\widehat{F}_s(s)-F_s(s)|\int_{s_0}^{L}|dH_n(s)|
\end{aligned}$$

Under Conditions (I), by the uniform consistency of $\widehat{F}_s(s)$ on $[s_0,L]$ and since $H_n(\cdot)$ is of bounded variation uniformly in n, the third term of (A.5) converges to zero in probability as $n \to \infty$. Therefore,

$$
\begin{aligned}
(A.5) \quad \xrightarrow{P} \quad & E\Big\{(1-R_i)\int_{s_0}^{L}\sum_{j=1}^{n_i} g_i(s+T_{ij})\xi_i^*(s,T_{ij})\frac{dF_s(s)}{F_s(V_i)}\Big\} \\
= \quad & E\Big\{(1-R_i)E_s\Big(\int_{t_1}^{t} g_i(u)dN_i^c(u) \mid \mathcal{D}_i, R_i=0\Big)\Big\} \\
= \quad & E\Big\{I(R_i=0)E_s\Big(\int_{t_1}^{t} g_i(u)dN_i^c(u) \mid \mathcal{D}_i, R_i=0\Big)\Big\} \\
= \quad & E\Big\{E_s\Big(I(R_i=0)\int_{t_1}^{t} g_i(u)dN_i^c(u) \mid \mathcal{D}_i, R_i=0\Big)\Big\} \\
= \quad & E\Big\{(1-R_i)\int_{t_1}^{t} g_i(u)dN_i^c(u)\Big\}
\end{aligned}
$$

The proof of Lemma A.2.1 is completed. □

Based on the above lemma, we can easily prove the following lemma.

Lemma A.2.2: Let $g(t,x,z,y)$ be a continuous function of (t,x,z,y) and $g_i(t) = g(t, X_i(t), Z_i(t), Y_i(t))$. Then under Conditions (I) and (II),

$$
n^{-1}\sum_{i=1}^{n} \ll \int_{t_1}^{t} g_i(u)dN_i^c(u) \gg_R \xrightarrow{P} E\Big\{\int_{t_1}^{t} g_i(u)dN_i^c(u)\Big\}
$$

uniformly in $t \in [t_1, t_2] \subset (0, \tau)$ as $n \to \infty$.

Proof. Note that

$$
\begin{aligned}
& n^{-1}\sum_{i=1}^{n} \ll \int_{t_1}^{t} g_i(u)dN_i^c(u) \gg_R \\
= \quad & n^{-1}\sum_{i=1}^{n} R_i\int_{t_1}^{t} g_i(u)dN_i^c(u) + n^{-1}\sum_{i=1}^{n}(1-R_i)\widehat{E}_s\Big\{\int_{t_1}^{t} g_i(u)dN_i^c(u) \mid \mathcal{X}\Big\} \\
= \quad & n^{-1}\sum_{i=1}^{n} R_i\int_{t_1}^{t} g_i(u)dN_i^c(u) + n^{-1}\sum_{i=1}^{n}(1-R_i)\widehat{E}_s\Big\{\int_{t_1}^{t} g_i(u)dN_i^c(u) \mid \mathcal{D}_i, R_i=0\Big\}.
\end{aligned}
\tag{A.6}
$$

By the law of large numbers, the first term of (A.6) converges to $E\{R_i \int_{t_1}^{t} g_i(u)dN_i^c(u)\}$

in probability and by Lemma A.2.1,

$$
\begin{aligned}
(A.6) \quad &\xrightarrow{P} \quad E\Big\{R_i \int_{t_1}^{t} g_i(u)dN_i^c(u)\Big\} + E\Big\{(1-R_i)\int_{t_1}^{t} g_i(u)dN_i^c(u)\Big\} \\
&= \quad E\Big\{R_i \int_{t_1}^{t} g_i(u)dN_i^c(u) + (1-R_i)\int_{t_1}^{t} g_i(u)dN_i^c(u)\Big\} \\
&= \quad E\Big\{\int_{t_1}^{t} g_i(u)dN_i^c(u)\Big\}.
\end{aligned}
$$

Lemma A.2.2 is proved. □

Lemma A.2.3: Let $g(t,x,z,y)$ be a continuous function of (t,x,z,y) and $g_i(t) = g(t, X_i(t), Z_i(t), Y_i(t))$. Then under Conditions (I) and (II),

$$
n^{-1}\sum_{i=1}^{n} \ll \int_0^{\tau} K_h(u-t)g_i(u)dN_i^c(u) \gg_R \xrightarrow{P} E(\xi_i(t)\alpha_i(t)g_i(t))
$$

uniformly in $t \in [t_1, t_2] \subset (0, \tau)$ as $n \to \infty$, $h \to 0$ and $nh^2 \to \infty$, where $\xi_i(t) = I(S_i + C_i \geq t)$.

Proof. By the definition,

$$
\begin{aligned}
& n^{-1}\sum_{i=1}^{n} \ll \int_0^{\tau} K_h(u-t)g_i(u)dN_i^c(u) \gg_R \\
= \; & n^{-1}\sum_{i=1}^{n} R_i \int_0^{\tau} K_h(u-t)g_i(u)dN_i^c(u) \\
& + n^{-1}\sum_{i=1}^{n}(1-R_i)\widehat{E}_s\Big\{\int_0^{\tau} K_h(u-t)g_i(u)dN_i^c(u) \mid \mathcal{X}\Big\} \qquad \text{(A.7)}
\end{aligned}
$$

Since the observations for different subjects are independent, the second term can be written as

$$
\begin{aligned}
& n^{-1}\sum_{i=1}^{n}(1-R_i)\widehat{E}_s\Big\{\int_0^{\tau} K_h(u-t)g_i(u)dN_i^c(u) \mid \mathcal{D}_i, R_i = 0\Big\} \\
= \; & n^{-1}\sum_{i=1}^{n}(1-R_i)\int_0^{\tau} K_h(u-t)d\Big(\int_0^{u} \widehat{E}_s\{g_i(v)dN_i^c(v) \mid \mathcal{D}_i, R_i = 0\}\Big). \text{(A.8)}
\end{aligned}
$$

It is easy to see that the convergence in Lemma A.2.1 holds uniformly in $u \in [0, \tau]$ with the interval $[0, u]$ in place of $[t_1, t_2]$. Then by the argument in the proof of Lemma

A.2.1,

$$n^{-1}\sum_{i=1}^{n}(1-R_i)\Big[\int_0^u \widehat{E}_s(g_i(v)dN_i^c(v)\mid \mathcal{D}_i, R_i=0)-\int_0^u E_s(g_i(v)dN_i^c(v)\mid \mathcal{D}_i, R_i=0)\Big]$$

converges to zero in probability uniformly in $u\in[0,\tau]$. So

$$\begin{aligned}
(A.8) &= \int_0^\tau K_h(u-t)d\Big(n^{-1}\sum_{i=1}^{n}(1-R_i)\int_0^u E_s\{g_i(v)dN_i^c(v)\mid \mathcal{D}_i, R_i=0\}\Big) \\
&\quad +o_p(1) \\
&= \int_0^\tau K_h(u-t)d\Big(E\Big[(1-R_i)\int_0^u E_s\{g_i(v)dN_i^c(v)\mid \mathcal{D}_i, R_i=0\}\Big]\Big)+o_p(1) \\
&= \int_0^\tau K_h(u-t)d\Big(\int_0^u E[E_s\{(1-R_i)g_i(v)dN_i^c(v)\mid \mathcal{D}_i, R_i=0\}]\Big)+o_p(1) \\
&= \int_0^\tau K_h(u-t)d\Big(\int_0^u E\{(1-R_i)g_i(v)dN_i^c(v)\}\Big)+o_p(1) \\
&= \int_0^\tau K_h(u-t)E\{(1-R_i)g_i(u)dN_i^c(u)\}+o_p(1).
\end{aligned}$$

According to the argument on Page 37 of Sun & Wu (2005), the first term of (A.7) is equal to

$$\int_0^\tau K_h(u-t)E\{R_i g_i(u)dN_i^c(u)\}+O_p(n^{-1/2}h^{-1}).$$

Note that $dN_i^c(u)=\xi_i(u)dN_i^o(u)$. Therefore,

$$\begin{aligned}
(A.7) &= \int_0^\tau K_h(u-t)E\{R_i g_i(u)dN_i^c(u)\}+\int_0^\tau K_h(u-t)E\{(1-R_i)g_i(u)dN_i^c(u)\} \\
&\quad +O_p(n^{-1/2}h^{-1})+o_p(1) \\
&= \int_0^\tau K_h(u-t)E\{g_i(u)dN_i^c(u)\}+O_p(n^{-1/2}h^{-1})+o_p(1) \\
&= \int_0^\tau K_h(u-t)E\{g_i(u)\xi_i(u)dN_i^o(u)\}+O_p(n^{-1/2}h^{-1})+o_p(1) \\
&= \int_0^\tau K_h(u-t)E\{\xi_i(u)E[g_i(u)dN_i^o(u)\mid X_i(u), Z_i(u), \xi_i(u)]\}+O_p(n^{-1/2}h^{-1}) \\
&\quad +o_p(1).
\end{aligned}$$

Since $Y_i(u)$ and $dN_i^o(u)$ are independent conditional on $X_i(u)$, $Z_i(u)$ and $\xi_i(u)$, by the assumptions of noninformative censoring,

$$
\begin{aligned}
(A.7) \quad = \quad & \int_0^\tau K_h(u-t)E\{\xi_i(u)E[g_i(u) \mid X_i(u), Z_i(u), \xi_i(u)] \\
& \quad E[dN_i^o(u) \mid X_i(u), Z_i(u), \xi_i(u)]\} + O_p(n^{-1/2}h^{-1}) + o_p(1) \\
= \quad & \int_0^\tau K_h(u-t)E\{\xi_i(u)E[g_i(u) \mid X_i(u), Z_i(u), \xi_i(u)]E[dN_i^o(u) \mid X_i(u), Z_i(u)]\} \\
& + O_p(n^{-1/2}h^{-1}) + o_p(1) \\
= \quad & \int_0^\tau K_h(u-t)E[\xi_i(u)E[g_i(u) \mid X_i(u), Z_i(u), \xi_i(u)]\alpha_i(u)du] + O_p(n^{-1/2}h^{-1}) \\
& + o_p(1) \\
= \quad & \int_0^\tau K_h(u-t)E(E[\xi_i(u)g_i(u)\alpha_i(u)du \mid X_i(u), Z_i(u)]) + O_p(n^{-1/2}h^{-1}) + o_p(1) \\
= \quad & \int_0^\tau K_h(u-t)E(\xi_i(u)g_i(u)\alpha_i(u)du) + O_p(n^{-1/2}h^{-1}) + o_p(1) \\
= \quad & E(\xi_i(t)\alpha_i(t)g_i(t)) + O(h^2) + O_p(n^{-1/2}h^{-1}) + o_p(1) \xrightarrow{P} E(\xi_i(t)\alpha_i(t)g_i(t))
\end{aligned}
$$

as $n \to \infty$, $h \to 0$ and $nh^2 \to \infty$. Lemma A.2.3 is proved. □

Define the counting process $N_i^*(t) = \sum_{j=1}^{n_i} I(T_{ij} \le t)I(C_i \ge t)$ and denote its mean rate by

$$E\{dN_i^*(t) \mid R_i, X_i(t), Y_i(t), Z_i(t), V_i\} = \alpha_i^*(t)dt. \tag{A.9}$$

Lemma A.2.4: Let $g(t, x, z, y)$ be a continuous function of (t, x, z, y) and $g_i(t) = g(t, X_i(t), Z_i(t), Y_i(t))$. Then under Conditions (I) and (II),

$$
\begin{aligned}
& n^{-1/2}h^{1/2}\sum_{i=1}^n (1-R_i)\widehat{E}_s\Big\{\int_0^\tau K_h(u-t)g_i(u)dN_i^c(u) \mid \mathcal{D}_i, R_i = 0\Big\} \\
- \quad & n^{-1/2}h^{1/2}\sum_{i=1}^n (1-R_i)E_s\Big\{\int_0^\tau K_h(u-t)g_i(u)dN_i^c(u) \mid \mathcal{D}_i, R_i = 0\Big\} = O_p(h^{1/2})
\end{aligned}
\tag{A.10}
$$

uniformly in $t \in [t_1, t_2] \subset (0, \tau)$ as $n \to \infty$, $h \to 0$ and $nh^2 \to \infty$.

Proof. The left side of (A.10) equals

$$
\begin{aligned}
& n^{-1/2}h^{1/2}\sum_{i=1}^{n}(1-R_i)\int_0^L\sum_{j=1}^{n_i}K_h(s+T_{ij}-t)g_i(s+T_{ij})I(C_i\ge T_{ij})I(s+T_{ij}\le\tau) \\
& \quad I(s\le V_i)\left(\frac{d\widehat{F}_s(s)}{\widehat{F}_s(V_i)}-\frac{dF_s(s)}{F_s(V_i)}\right) \\
= {} & n^{-1}h^{1/2}\sum_{i=1}^{n}\int_0^L\int_0^\tau(1-R_i)K_h(v-t)g_i(v)dN_i^*(v-s)I(s\le V_i) \\
& \quad \frac{n^{1/2}(\widehat{S}_s(V_i)-S_s(V_i))}{F_s^2(V_i)}dF_s(s) \\
& -n^{-1}h^{1/2}\sum_{i=1}^{n}\int_0^L\int_0^\tau(1-R_i)K_h(v-t)g_i(v)dN_i^*(v-s)I(s\le V_i) \\
& \quad \frac{d\{n^{1/2}(\widehat{S}_s(V_i)-S_s(V_i))\}}{F_s(V_i)}.
\end{aligned}
$$

Applying (A.1),above equation equals

$$
\begin{aligned}
& n^{-1}h^{1/2}\sum_{i=1}^{n}\int_0^L\int_0^\tau(1-R_i)K_h(v-t)g_i(v)dN_i^*(v-s)I(s\le V_i) \\
& \quad \frac{n^{-1/2}}{F_s(V_i)}\int_0^{(L-V_i)-}\frac{dM^S(x)}{y^S(x)}dF_s(s) \\
& -n^{-1}h^{1/2}\sum_{i=1}^{n}\int_0^L\int_0^\tau(1-R_i)K_h(v-t)g_i(v)dN_i^*(v-s)I(s\le V_i) \\
& \quad \frac{1}{F_s(V_i)}d\left\{n^{-1/2}F_s(s)\int_0^{(L-s)-}\frac{dM^S(x)}{y^S(x)}\right\}+o_p(1) \\
= {} & h^{1/2}n^{-1/2}\int_0^\infty\int_0^L\int_0^\tau K_h(v-t)n^{-1}\sum_{i=1}^{n}(1-R_i)g_i(v)dN_i^*(v-s)I(s\le V_i) \\
& \quad \frac{I(x<(L-V_i)-)}{F_s(V_i)}dF_s(s)\frac{dM^S(x)}{y^S(x)} \\
& -h^{1/2}n^{-1/2}\int_0^L\int_0^\tau K_h(v-t)n^{-1}\sum_{i=1}^{n}(1-R_i)g_i(v)\frac{dN_i^*(v-s)}{F_s(V_i)}I(s\le V_i) \\
& \quad F_s(s)\frac{dM^S((L-s)-)}{y^S((L-s)-)} \\
& -h^{1/2}n^{-1/2}\int_0^L\int_0^{(L-x)-}\int_0^\tau K_h(v-t)n^{-1}\sum_{i=1}^{n}(1-R_i)g_i(v)\frac{dN_i^*(v-s)}{F_s(V_i)}I(s\le V_i) \\
& \quad dF_s(s)\frac{dM^S(x)}{y^S(x)}. \qquad\qquad (A.11)
\end{aligned}
$$

Let $u = v - s$. The third term of (A.11) is

$$h^{1/2}n^{-1/2}\int_0^\tau K_h(v-t)n^{-1}\sum_{i=1}^n(1-R_i)g_i(v)\int_0^L\int_0^{(L-x)-}\frac{dN_i^*(v-s)}{F_s(V_i)}I(s\le V_i)$$
$$dF_s(s)\frac{dM^S(x)}{y^S(x)}$$
$$= h^{1/2}n^{-1/2}\int_0^L\int_{-s}^{\tau-s}K_h(u+s-t)n^{-1}\sum_{i=1}^n(1-R_i)g_i(u+s)\frac{dN_i^*(u)}{F_s(V_i)}I(s\le V_i)$$
$$\int_0^{(L-s)-}\frac{dM^S(x)}{y^S(x)}dF_s(s). \quad \text{(A.12)}$$

Let

$$\Gamma_n(s) = \int_{-s}^{\tau-s}K_h(u+s-t)n^{-1}\sum_{i=1}^n(1-R_i)g_i(u+s)\frac{dN_i^*(u)}{F_s(V_i)}I(s\le V_i).$$

Then $(A.12) = h^{1/2}n^{-1/2}\int_0^L\Gamma_n(s)\int_0^{(L-s)-}\frac{dM^S(x)}{y^S(x)}dF_s(s)$. Note that

$$E(\Gamma_n(s)) = \int_{-s}^{\tau-s}K_h(u+s-t)E\Big\{(1-R_i)g_i(u+s)\frac{\alpha_i^*(u)}{F_s(V_i)}I(s\le V_i)\Big\}du$$
$$\to E\Big\{(1-R_i)g_i(t)\frac{\alpha_i^*(t-s)}{F_s(V_i)}I(s\le V_i)\Big\}, \quad \text{(A.13)}$$

uniformly in t and s as $n\to\infty$ and $h\to 0$, and by applying Lemma A.1 of Lin & Ying (2001) we have

$$\Gamma_n(s) - E(\Gamma_n(s))$$
$$= \int_{-s}^{\tau-s}n^{-1/2}K_h(u+s-t)n^{1/2}d\Big\{\int_{-s}^u n^{-1}\sum_{i=1}^n(1-R_i)g_i(v+s)\frac{dN_i^*(v)}{F_s(V_i)}I(s\le V_i)$$
$$-\int_{-s}^u E\Big\{(1-R_i)g_i(v+s)\frac{\alpha_i^*(v)}{F_s(V_i)}I(s\le V_i)dv\Big\}$$
$$\xrightarrow{P} 0,$$

uniformly in t and s as $n\to\infty$, $h\to 0$ and $nh^2\to\infty$. Hence (A.12) equals

$$h^{1/2}n^{-1/2}\int_0^L E(\Gamma_n(s))\int_0^{(L-s)-}\frac{dM^S(x)}{y^S(x)}dF_s(s) + o_p(h^{1/2})$$
$$= h^{1/2}n^{-1/2}\int_0^L E\Big\{(1-R_i)g_i(t)\frac{\alpha_i^*(t-s)}{F_s(V_i)}I(s\le V_i)\Big\}\int_0^{(L-s)-}\frac{dM^S(x)}{y^S(x)}dF_s(s)$$

$$
\begin{aligned}
& +o_p(h^{1/2}) \\
= \;& h^{1/2}n^{-1/2}\int_0^L\int_0^{(L-x)-} E\left\{(1-R_i)g_i(t)\frac{\alpha_i^*(t-s)}{F_s(V_i)}I(s\le V_i)\right\}dF_s(s)\frac{dM^S(x)}{y^S(x)} \\
& +o_p(h^{1/2}) \\
= \;& O_p(h^{1/2})+o_p(h^{1/2}). \qquad \text{(A.14)}
\end{aligned}
$$

Now apply similar arguments to the first and second terms of (A.11), we can obtain the left side of (A.10) is of the order of $O_p(h^{1/2})$. Lemma has been proved. □

Further, if $E\{g_i(t) \mid R_i, V_i, \alpha_i^*(t-s)\} = 0$ for $s \le t$, then (A.10) holds at the rate of $o_p(h^{1/2})$.

Lemma A.2.5: Under Conditions (I) and (II),

$$
\begin{aligned}
& n^{1/2}\int_{t_1}^t \{\tilde{E}_{zx}(u)-e_{zx}(u)\}(e_{xx}(u))^{-1}du \\
= \;& n^{-1/2}\sum_{i=1}^n\int_{t_1}^t\left[d\{X_{zi}^I(v)+X_{zi}^{II}(v)+X_{zi}^{III}(v)\}(e_{xx}(v))^{-1}\right] \\
& +O_p(n^{-1/2}h^2+n^{1/2}h^2)+o_p(1) \qquad \text{(A.15)}
\end{aligned}
$$

converges weakly to a vector of mean-zero Gaussian processes with continuous paths as $n\to\infty$, $h\to 0$ and $nh^4\to 0$. Similar results hold for

$$
\begin{aligned}
& n^{1/2}\int_{t_1}^t \{\tilde{E}_{yx}(u)-e_{yx}(u)\}(e_{xx}(u))^{-1}du \\
= \;& n^{-1/2}\sum_{i=1}^n\int_{t_1}^t\left[d\{X_{yi}^I(v)+X_{yi}^{II}(v)+X_{yi}^{III}(v)\}(e_{xx}(v))^{-1}\right] \\
& +O_p(n^{-1/2}h^2+n^{1/2}h^2)+o_p(1), \qquad \text{(A.16)}
\end{aligned}
$$

$$
\begin{aligned}
& n^{1/2}\int_{t_1}^t \beta^T(u)\{\tilde{E}_{xx}(u)-e_{xx}(u)\}(e_{xx}(u))^{-1}du \\
= \;& n^{-1/2}\sum_{i=1}^n\int_{t_1}^t\left[\beta^T(u)d\{X_{xi}^I(v)+X_{xi}^{II}(v)+X_{xi}^{III}(v)\}(e_{xx}(v))^{-1}\right] \\
& +O_p(n^{-1/2}h^2+n^{1/2}h^2)+o_p(1). \qquad \text{(A.17)}
\end{aligned}
$$

Proof. By the definitions,

$$
\begin{aligned}
& n^{1/2}\int_{t_1}^{t}(\tilde{E}_{zx}(u)-e_{zx}(u))(e_{xx}(u))^{-1}du \\
= \;& n^{1/2}\int_{t_1}^{t}\Bigg(n^{-1}\sum_{i=1}^{n}\ll\int_0^{\tau}K_h(v-u)Z_i(v)X_i^T(v)dN_i^c(v)\gg_R \\
& \quad -E\{\xi_i(u)\alpha_i(u)Z_i(u)X_i^T(u)\}\Bigg)(e_{xx}(u))^{-1}du \\
= \;& n^{-1/2}\sum_{i=1}^{n}\int_{t_1}^{t}\Bigg[R_i\int_0^{\tau}K_h(v-u)Z_i(v)X_i^T(v)dN_i^c(v) \\
& \quad -E\{R_i\xi_i(u)\alpha_i(u)Z_i(u)X_i^T(u)\} \\
& +(1-R_i)\widehat{E}_s\Big\{\int_0^{\tau}K_h(v-u)Z_i(v)X_i^T(v)dN_i^c(v)\mid\mathcal{X}\Big\} \\
& \quad -E\{(1-R_i)\xi_i(u)\alpha_i(u)Z_i(u)X_i^T(u)\}\Bigg](e_{xx}(u))^{-1}du \\
= \;& n^{-1/2}\sum_{i=1}^{n}\int_{t_1}^{t}\Bigg[R_i\int_0^{\tau}K_h(v-u)Z_i(v)X_i^T(v)dN_i^c(v) \\
& \quad -E\{R_i\xi_i(u)\alpha_i(u)Z_i(u)X_i^T(u)\} \\
& +(1-R_i)\widehat{E}_s\Big\{\int_0^{\tau}K_h(v-u)Z_i(v)X_i^T(v)dN_i^c(v)\mid\mathcal{D}_i,R_i=0\Big\} \\
& \quad -E\{(1-R_i)\xi_i(u)\alpha_i(u)Z_i(u)X_i^T(u)\}\Bigg](e_{xx}(u))^{-1}du \\
= \;& n^{-1/2}\sum_{i=1}^{n}\int_{t_1}^{t}\Bigg[R_i\int_0^{\tau}K_h(v-u)Z_i(v)X_i^T(v)dN_i^c(v) \\
& \quad -E\{R_i\xi_i(u)\alpha_i(u)Z_i(u)X_i^T(u)\}\Bigg](e_{xx}(u))^{-1}du \\
& +n^{-1/2}\sum_{i=1}^{n}\int_{t_1}^{t}(1-R_i)\Bigg[\widehat{E}_s\Big\{\int_0^{\tau}K_h(v-u)Z_i(v)X_i^T(v)dN_i^c(v)\mid\mathcal{D}_i,R_i=0\Big\} \\
& \quad -E_s\Big\{\int_0^{\tau}K_h(v-u)Z_i(v)X_i^T(v)dN_i^c(v)\mid\mathcal{D}_i,R_i=0\Big\}\Bigg](e_{xx}(u))^{-1}du \\
& +n^{-1/2}\sum_{i=1}^{n}\int_{t_1}^{t}\Bigg[(1-R_i)E_s\Big\{\int_0^{\tau}K_h(v-u)Z_i(v)X_i^T(v)dN_i^c(v)\mid\mathcal{D}_i,R_i=0\Big\} \\
& \quad -E\{(1-R_i)\xi_i(u)\alpha_i(u)Z_i(u)X_i^T(u)\}\Bigg](e_{xx}(u))^{-1}du \\
= \;& n^{-1/2}\sum_{i=1}^{n}\int_{t_1}^{t}\Bigg[\int_0^{\tau}R_iK_h(v-u)Z_i(v)X_i^T(v)dN_i^c(v)
\end{aligned}
$$

$$
\begin{aligned}
&-E\{R_i\xi_i(u)\alpha_i(u)Z_i(u)X_i^T(u)\}\Big](e_{xx}(u))^{-1}du \\
&+n^{-1/2}\sum_{i=1}^{n}\int_{t_1}^{t}(1-R_i)\int_0^L\sum_{j=1}^{n_i}K_h(s+T_{ij}-u)Z_{ij}X_{ij}^T I(C_i\geq T_{ij})\Big[\frac{d\widehat{F}_s(s\mid\mathcal{D}_i)}{\widehat{F}_s(V_i\mid\mathcal{D}_i)} \\
&-\frac{dF_s(s\mid\mathcal{D}_i)}{F_s(V_i\mid\mathcal{D}_i)}\Big](e_{xx}(u))^{-1}du \\
&+n^{-1/2}\sum_{i=1}^{n}\int_{t_1}^{t}\Big[(1-R_i)E_s\Big\{\int_0^\tau K_h(v-u)Z_i(v)X_i^T(v)dN_i^c(v)\mid\mathcal{D}_i,R_i=0\Big\} \\
&-E\{(1-R_i)\xi_i(u)\alpha_i(u)Z_i(u)X_i^T(u)\}\Big](e_{xx}(u))^{-1}du. \qquad \text{(A.18)}
\end{aligned}
$$

Denote the three terms in (A.18) by A, B and C, respectively. Then

$$
\begin{aligned}
A &= n^{-1/2}\sum_{i=1}^{n}\int_{t_1}^{t}\Big[\int_0^\tau K_h(v-u)R_iZ_i(v)X_i^T(v)dN_i^c(v) \\
&\quad -\int_0^\tau K_h(v-u)E\{R_i\xi(v)\alpha_i(v)Z_i(v)X_i^T(v)\}dv+O(h^2)\Big](e_{xx}(u))^{-1}du \\
&= n^{-1/2}\sum_{i=1}^{n}\int_{t_1}^{t}\int_0^\tau K_h(v-u)[R_iZ_i(v)X_i^T(v)dN_i^c(v) \\
&\quad -E\{R_i\xi(v)\alpha_i(v)Z_i(v)X_i^T(v)\}dv](e_{xx}(u))^{-1}du+O_p(n^{1/2}h^2) \\
&= n^{1/2}\int_{t_1}^{t}\int_0^\tau K_h(v-u)n^{-1}\sum_{i=1}^{n}[R_iZ_i(v)X_i^T(v)dN_i^c(v) \\
&\quad -E\{R_i\xi(v)\alpha_i(v)Z_i(v)X_i^T(v)\}dv](e_{xx}(u))^{-1}du+O_p(n^{1/2}h^2) \\
&= \int_{t_1}^{t}\int_0^\tau K_h(v-u)d\Big(n^{-1/2}\sum_{i=1}^{n}\int_0^v[R_iZ_i(w)X_i^T(w)dN_i^c(w) \\
&\quad -E\{R_i\xi_i(w)\alpha_i(w)Z_i(w)X_i^T(w)\}dw]\Big)(e_{xx}(u))^{-1}du+O_p(n^{1/2}h^2). \qquad \text{(A.19)}
\end{aligned}
$$

Note that

$$
X_{zn}^I(v)=n^{-1/2}\sum_{i=1}^{n}\int_0^v[R_iZ_i(w)X_i^T(w)dN_i^c(w)-E\{R_i\xi_i(w)\alpha_i(w)Z_i(w)X_i^T(w)\}dw].
$$

Under Condition (I) $X_{zn}^I(v)$ converges to a vector of mean zero Gaussian processes, saying $X_z^I(v)$ uniformly in v. Then also by the compactness of $K(\cdot)$ and the application of the continuous mapping theorem,

$$\begin{aligned}
A &= \int_{t_1}^{t}\int_{0}^{\tau} K_h(v-u)dX_{zn}^{I}(v)(e_{xx}(u))^{-1}du + O_p(n^{1/2}h^2) \\
&= \int_{t_1-h}^{t+h}\left[dX_{zn}^{I}(v)\int_{t_1}^{t} h^{-1}K(\frac{v-u}{h})(e_{xx}(u))^{-1}du\right] + O_p(n^{1/2}h^2) \\
&= \int_{t_1-h}^{t+h}\left[dX_{zn}^{I}(v)((e_{xx}(v))^{-1} + O(h^2))\right] + O_p(n^{1/2}h^2) \\
&\xrightarrow{D} \int_{t_1}^{t}\left[dX_{z}^{I}(v)((e_{xx}(v))^{-1})\right] \qquad \text{(A.20)}
\end{aligned}$$

as $n \to \infty$, $h \to 0$ and $nh^4 \to 0$.

The third summation in (A.18)

$$\begin{aligned}
C &= n^{-1/2}\sum_{i=1}^{n}\int_{t_1}^{t}\Bigg[\int_{0}^{\tau} K_h(v-u)E_s\{(1-R_i)Z_i(v)X_i^T(v)dN_i^c(v) \mid \mathcal{D}_i, R_i = 0\} \\
&\quad -E\{(1-R_i)\xi_i(u)\alpha_i(u)Z_i(u)X_i^T(u)\}\Bigg](e_{xx}(u))^{-1}du \\
&= n^{-1/2}\sum_{i=1}^{n}\int_{t_1}^{t}\Bigg[\int_{0}^{\tau} K_h(v-u)E_s\{(1-R_i)Z_i(v)X_i^T(v)dN_i^c(v) \mid \mathcal{D}_i, R_i = 0\} \\
&\quad -\int_{0}^{\tau} K_h(v-u)E\{(1-R_i)\xi_i(v)\alpha_i(v)Z_i(v)X_i^T(v)\}dv + O(h^2)\Bigg] \\
&\quad (e_{xx}(u))^{-1}du \\
&= \int_{t_1}^{t}\Bigg[\int_{0}^{\tau} K_h(v-u)\Bigg\{n^{-1/2}\sum_{i=1}^{n}(E_s\{(1-R_i)Z_i(v)X_i^T(v)dN_i^c(v) \mid \mathcal{D}_i, R_i = 0\} \\
&\quad -E\{(1-R_i)\xi_i(v)\alpha_i(v)Z_i(v)X_i^T(v)\}dv)\Bigg\}\Bigg](e_{xx}(u))^{-1}du + O_p(n^{1/2}h^2) \\
&= \int_{t_1}^{t}\Bigg[\int_{0}^{\tau} K_h(v-u)d\Bigg\{n^{-1/2}\sum_{i=1}^{n}\int_{0}^{v}(E_s\{(1-R_i)Z_i(w)X_i^T(w)dN_i^c(w) \mid \mathcal{D}_i, R_i \\
&\quad = 0\} - E\{(1-R_i)\xi_i(w)\alpha_i(w)Z_i(w)X_i^T(w)\}dw)\Bigg\}\Bigg](e_{xx}(u))^{-1}du \\
&\quad +O_p(n^{1/2}h^2). \qquad \text{(A.21)}
\end{aligned}$$

Note that

$$\begin{aligned}
X_{zn}^{III}(v) &= n^{-1/2}\sum_{i=1}^{n}\int_{0}^{v}(E_s\{(1-R_i)Z_i(w)X_i^T(w)dN_i^c(w) \mid \mathcal{D}_i, R_i = 0\} \\
&\quad -E\{(1-R_i)\xi_i(w)\alpha_i(w)Z_i(w)X_i^T(w)\}dw).
\end{aligned}$$

Under Condition (I) $X_{zn}^{III}(v)$ converges to a vector of mean zero Gaussian processes, saying $X_z^{III}(v)$ uniformly in v. Following similar arguments in deriving (A.20) for the term A, we have

$$\begin{aligned} C &= \int_{t_1}^{t}\int_0^{\tau} K_h(v-u)dX_{zn}^{III}(v)(e_{xx}(u))^{-1}du + O_p(n^{1/2}h^2) \\ &= \int_{t_1-h}^{t+h}\left[\{dX_{zn}^{III}(v)\}((e_{xx}(v))^{-1}+O(h^2))\right] + O_p(n^{1/2}h^2) \\ &\xrightarrow{D} \int_{t_1}^{t}\left[\{dX_z^{III}(v)\}((e_{xx}(v))^{-1})\right] \end{aligned} \tag{A.22}$$

as $n\to\infty$, $h\to 0$ and $nh^4\to 0$.

Remind the counting process $N_i^*(t)=\sum_{j=1}^{n_i} I(T_{ij}\le t)I(C_i\ge t)$ and its mean rate $E\{dN_i^*(t)\mid R_i, X_i(t), Y_i(t), Z_i(t), V_i\}=\alpha_i^*(t)dt$. The second summation of (A.18)

$$\begin{aligned} B &= n^{-1/2}\sum_{i=1}^{n}\int_{t_1}^{t}(1-R_i)\int_0^{L}\sum_{j=1}^{n_i}K_h(s+T_{ij}-u)Z_{ij}X_{ij}^TI(C_i\ge T_{ij})\left[\frac{d\widehat{F}_s(s)}{\widehat{F}_s(V_i)}\right. \\ &\quad \left.-\frac{dF_s(s)}{F_s(V_i)}\right](e_{xx}(u))^{-1}du \\ &= n^{-1/2}\sum_{i=1}^{n}\int_{t_1}^{t}(1-R_i)\int_0^{L}\int_0^{\tau}K_h(v-u)Z_i(v)X_i^T(v)dN_i^*(v-s)\left[\left(\frac{1}{\widehat{F}_s(V_i)}\right.\right. \\ &\quad \left.\left.-\frac{1}{F_s(V_i)}\right)dF_s(s)+\frac{d\widehat{F}_s(s)-dF_s(s)}{\widehat{F}_s(V_i)}\right](e_{xx}(u))^{-1}du \\ &= n^{-1/2}\sum_{i=1}^{n}\int_{t_1}^{t}(1-R_i)\int_0^{L}\int_0^{\tau}K_h(v-u)Z_i(v)X_i^T(v)dN_i^*(v-s)\frac{F_s(V_i)-\widehat{F}_s(V_i)}{F_s^2(V_i)} \\ &\quad dF_s(s)(e_{xx}(u))^{-1}du \\ &\quad +n^{-1/2}\sum_{i=1}^{n}\int_{t_1}^{t}(1-R_i)\int_0^{L}\int_0^{\tau}K_h(v-u)Z_i(v)X_i^T(v)dN_i^*(v-s) \\ &\quad \frac{d(\widehat{F}_s(s)-F_s(s))}{F_s(V_i)}(e_{xx}(u))^{-1}du+o_p(1) \\ &= n^{-1}\sum_{i=1}^{n}\int_{t_1}^{t}\int_0^{L}\int_0^{\tau}(1-R_i)K_h(v-u)Z_i(v)X_i^T(v)dN_i^*(v-s) \\ &\quad \frac{n^{1/2}(\widehat{S}_s(V_i)-S_s(V_i))}{F_s^2(V_i)}dF_s(s)(e_{xx}(u))^{-1}du \\ &\quad -n^{-1}\sum_{i=1}^{n}\int_{t_1}^{t}(1-R_i)\int_0^{L}\int_0^{\tau}K_h(v-u)Z_i(v)X_i^T(v)dN_i^*(v-s) \end{aligned}$$

$$\frac{d[n^{1/2}(\widehat{S}_s(s)-S_s(s))]}{F_s(V_i)}(e_{xx}(u))^{-1}du \tag{A.23}$$
$$+o_p(1)$$

Applying the approximation (A.1), the first term of (A.23) is

$$\begin{aligned}
& n^{-1}\sum_{i=1}^{n}\int_{t_1}^{t}\int_0^L\int_0^\tau (1-R_i)K_h(v-u)Z_i(v)X_i^T(v)dN_i^*(v-s)\frac{n^{-1/2}F_s(V_i)}{F_s^2(V_i)} \\
& \quad \int_0^{(L-(V_i))-}\frac{dM^S(x)}{y^S(x)}dF_s(s)(e_{xx}(u))^{-1}du+o_p(1) \\
= & \int_{t_1}^{t}\int_0^L n^{-1}\sum_{i=1}^{n}\int_0^\tau (1-R_i)K_h(v-u)Z_i(v)X_i^T(v)dN_i^*(v-s)\frac{n^{-1/2}}{F_s(V_i)} \\
& \quad \int_0^\infty I(x\le (L-(V_i))-)\frac{dM^S(x)}{y^S(x)}dF_s(s)(e_{xx}(u))^{-1}du+o_p(1) \\
= & n^{-1/2}\int_0^\infty\int_0^L\int_{t_1}^{t}\int_0^\tau K_h(v-u)n^{-1}\sum_{i=1}^{n}(1-R_i)Z_i(v)X_i^T(v)dN_i^*(v-s) \\
& \quad \frac{I(x\le (L-(V_i))-)}{F_s(V_i)}(e_{xx}(u))^{-1}dudF_s(s)\frac{dM^S(x)}{y^S(x)}+o_p(1).
\end{aligned} \tag{A.24}$$

The second term of (A.23) is

$$\begin{aligned}
& -n^{-1}\sum_{i=1}^{n}\int_{t_1}^{t}(1-R_i)\int_0^L\int_0^\tau K_h(v-u)\frac{Z_i(v)X_i^T(v)dN_i^*(v-s)}{F_s(V_i)} \\
& \quad d\Big\{n^{-1/2}F_s(s)\int_0^{(L-s)-}\frac{dM^S(x)}{y^S(x)}\Big\}(e_{xx}(u))^{-1}du+o_p(1) \\
= & -n^{-1}\sum_{i=1}^{n}\int_{t_1}^{t}(1-R_i)\int_0^L\int_0^\tau K_h(v-u)\frac{Z_i(v)X_i^T(v)dN_i^*(v-s)}{F_s(V_i)} \\
& \quad n^{-1/2}\int_0^{(L-s)-}\frac{dM^S(x)}{y^S(x)}dF_s(s)(e_{xx}(u))^{-1}du \\
& +n^{-1}\sum_{i=1}^{n}\int_{t_1}^{t}(1-R_i)\int_0^L\int_0^\tau K_h(v-u)\frac{Z_i(v)X_i^T(v)dN_i^*(v-s)}{F_s(V_i)}n^{-1/2}F_s(s) \\
& \quad \frac{dM^S((L-s)-)}{y^S((L-s)-)}(e_{xx}(u))^{-1}du+o_p(1) \\
= & -n^{-1/2}\int_0^{L-}\int_0^{(L-x)-}\int_{t_1}^{t}\int_0^\tau K_h(v-u)n^{-1}\sum_{i=1}^{n}(1-R_i)\frac{Z_i(v)X_i^T(v)}{F_s(V_i)} \\
& \quad dN_i^*(v-s)(e_{xx}(u))^{-1}du\,dF_s(s)\frac{dM^S(x)}{y^S(x)}
\end{aligned}$$

$$+n^{-1/2}\int_0^L\int_{t_1}^t\int_0^\tau K_h(v-u)n^{-1}\sum_{i=1}^n(1-R_i)\frac{Z_i(v)X_i^T(v)dN_i^*(v-s)}{F_s(V_i)}F_s(s)$$
$$(e_{xx}(u))^{-1}du\frac{dM^S((L-s)-)}{y^S((L-s)-)}+o_p(1). \tag{A.25}$$

Since

$$\begin{aligned}
&\int_0^\tau K_h(v-u)n^{-1}\sum_{i=1}^n(1-R_i)Z_i(v)X_i^T(v)dN_i^*(v-s)\frac{I(x\le(L-(V_i))-)}{F_s(V_i)}\\
=&\int_0^\tau K_h(v-u)d\Big(n^{-1}\sum_{i=1}^n\int_0^v(1-R_i)Z_i(w)X_i^T(w)dN_i^*(w-s)\\
&\quad\frac{I(x\le(L-(V_i))-)}{F_s(V_i)}\Big)\\
=&\int_0^\tau K_h(v-u)dE\Big\{\int_0^v(1-R_i)Z_i(w)X_i^T(w)dN_i^*(w-s)\frac{I(x\le(L-(V_i))-)}{F_s(V_i)}\Big\}\\
&+o_p(1)\\
=&\int_0^\tau K_h(v-u)dE\Big\{E\Big[\int_0^v(1-R_i)Z_i(w)X_i^T(w)dN_i^*(w-s)\\
&\quad\frac{I(x\le(L-(V_i))-)}{F_s(V_i)}\Big|R_i,X_i(\cdot),Y_i(\cdot),Z_i(\cdot),V_i\Big]\Big\}+o_p(1)\\
=&\int_0^\tau K_h(v-u)dE\Big\{\int_0^v(1-R_i)Z_i(w)X_i^T(w)E[dN_i^*(w-s)\mid R_i,X_i(\cdot),Y_i(\cdot),\\
&\quad Z_i(\cdot),V_i]\frac{I(x\le(L-(V_i))-)}{F_s(V_i)}\Big\}+o_p(1)\\
=&\int_0^\tau K_h(v-u)dE\Big\{\int_0^v(1-R_i)Z_i(w)X_i^T(w)\alpha_i^*(w-s)dw\frac{I(x\le(L-(V_i))-)}{F_s(V_i)}\Big\}\\
&+o_p(1)\\
=&\int_0^\tau K_h(v-u)E\Big\{(1-R_i)Z_i(v)X_i^T(v)\alpha_i^*(v-s)\frac{I(x\le(L-(V_i))-)}{F_s(V_i)}\Big\}dv+o_p(1)\\
=&E\Big\{(1-R_i)Z_i(u)X_i^T(u)\alpha_i^*(u-s)\frac{I(x\le(L-(V_i))-)}{F_s(V_i)}\Big\}+O_p(h^2)+o_p(1)
\end{aligned} \tag{A.26}$$

and similarly

$$\begin{aligned}
&\int_0^\tau K_h(v-u)n^{-1}\sum_{i=1}^n(1-R_i)\frac{Z_i(v)X_i^T(v)dN_i^*(v-s)}{F_s(V_i)}\\
=&E\Big\{(1-R_i)\frac{Z_i(u)X_i^T(u)\alpha_i^*(u-s)}{F_s(V_i)}\Big\}+O_p(h^2)+o_p(1),
\end{aligned}$$

then

$$
\begin{aligned}
(A.24) &= n^{-1/2}\int_0^\infty\int_0^L\int_{t_1}^t E\Big\{(1-R_i)Z_i(u)X_i^T(u)\alpha_i^*(u-s)\frac{I(x\le(L-(V_i))-)}{F_s(V_i)}\Big\}\\
&\qquad (e_{xx}(u))^{-1}du\,dF_s(s)\frac{dM^S(x)}{y^S(x)}+O_p(n^{-1/2}h^2)+o_p(1),\\
(A.25) &= -n^{-1/2}\int_0^{L-}\int_0^{(L-x)-}\int_{t_1}^t E\Big\{(1-R_i)\frac{Z_i(u)X_i^T(u)\alpha_i^*(u-s)}{F_s(V_i)}\Big\}(e_{xx}(u))^{-1}\\
&\qquad du\,dF_s(s)\frac{dM^S(x)}{y^S(x)}\\
&\quad +n^{-1/2}\int_0^L\int_{t_1}^t E\Big\{(1-R_i)\frac{Z_i(u)X_i^T(u)\alpha_i^*(u-s)}{F_s(V_i)}\Big\}F_s(s)(e_{xx}(u))^{-1}\\
&\qquad du\frac{dM^S((L-s)-)}{y^S((L-s)-)}+O_p(n^{-1/2}h^2)+o_p(1)
\end{aligned}
$$

Hence the second summation of (A.18)

$$
\begin{aligned}
B &= n^{-1/2}\Big[\int_0^\infty\int_0^L\int_{t_1}^t E\Big\{(1-R_i)Z_i(u)X_i^T(u)\alpha_i^*(u-s)\frac{I(x\le(L-V_i)-)}{F_s(V_i)}\Big\}\\
&\qquad (e_{xx}(u))^{-1}du\,dF_s(s)\frac{dM^S(x)}{y^S(x)}\\
&\quad -\int_0^{L-}\int_0^{(L-x)-}\int_{t_1}^t E\Big\{(1-R_i)\frac{Z_i(u)X_i^T(u)\alpha_i^*(u-s)}{F_s(V_i)}\Big\}(e_{xx}(u))^{-1}du\\
&\qquad dF_s(s)\frac{dM^S(x)}{y^S(x)}\\
&\quad +\int_0^L\int_{t_1}^t E\Big\{(1-R_i)\frac{Z_i(u)X_i^T(u)\alpha_i^*(u-s)}{F_s(V_i)}\Big\}F_s(s)(e_{xx}(u))^{-1}du\\
&\qquad \frac{dM^S((L-s)-)}{y^S((L-s)-)}\Big]+O_p(n^{-1/2}h^2)+o_p(1)\\
&= \int_{t_1}^t(dX_{zn}^{II}(v))(e_{xx}(v))^{-1}+O_p(n^{-1/2}h^2)+o_p(1). \qquad (A.27)
\end{aligned}
$$

The asymptotic approximation (A.15) follows from (A.18), (A.20), (A.22) and (A.27). The weak convergence of (A.15) follows from application of the Donsker Theorem (c.f., van der Vaart and Wellner, 1996 and Lemma 1 of Sun and Wu (2005)). □

Recall the definitions in Section A.1. We can have the following lemma.

Lemma A.2.6: Under Conditions (I) and (II), $n^{1/2}\int_{t_1}^t\{\tilde{Z}_x(u)-z_x(u)\}du$ and $n^{1/2}\int_{t_1}^t\{\tilde{Y}_x(u)-$

$y_x(u)\}du$ converge weakly to mean zero Gaussian processes with continuous paths as $n \to \infty$, $h \to 0$ and $nh^4 \to 0$. Futher,

$$\begin{aligned}
& n^{1/2}\int_{t_1}^{t}\{\tilde{\beta}^T(u,\gamma_0) - \beta_0^T(u)\}du \\
= \;& n^{-1/2}\sum_{i=1}^{n}\Big\{\int_{t_1}^{t} d(X_{yi}^{I}(v) + X_{yi}^{II}(v) + X_{yi}^{III}(v))(e_{xx}(v))^{-1} \\
& \quad - \int_{t_1}^{t}\gamma_0^T d(X_{zi}^{I}(v) + X_{zi}^{II}(v) + X_{zi}^{III}(v))(e_{xx}(v))^{-1} \\
& \quad - \int_{t_1}^{t}\beta^T(v) d(X_{xi}^{I}(v) + X_{xi}^{II}(v) + X_{xi}^{III}(v))(e_{xx}(v))^{-1}\Big\} \\
& + O_p(n^{-1/2}h^2 + n^{1/2}h^2) + o_p(1) \qquad \text{(A.28)}
\end{aligned}$$

converges weakly to a mean zero Gaussian process with continuous paths as $n \to \infty$, $h \to 0$ and $nh^4 \to 0$.

Proof. By the definitions,

$$\begin{aligned}
& n^{1/2}\int_{t_1}^{t}\{\tilde{\beta}^T(u,\gamma_0) - \beta_0^T(u)\}du \\
= \;& \int_{t_1}^{t} n^{1/2}\{\tilde{Y}_x(u) - \gamma_0^T\tilde{Z}_x(u) - (y_x(u) - \gamma_0^T z_x(u))\}du \\
= \;& n^{1/2}\int_{t_1}^{t}\{\tilde{Y}_x(u) - y_x(u)\}du - \gamma_0^T n^{1/2}\int_{t_1}^{t}\{\tilde{Z}_x(u) - z_x(u)\}du \qquad \text{(A.29)}
\end{aligned}$$

By the continuous mapping theorem, it is sufficient to prove that

$$\left(n^{1/2}\int_{t_1}^{t}\{\tilde{Y}_x(u) - y_x(u)\}du,\; n^{1/2}\int_{t_1}^{t}\{\tilde{Z}_x(u) - z_x(u)\}du\right) \qquad \text{(A.30)}$$

converges weakly to a vector of mean zero Gaussian processes with continuous sample paths. Note that

$$\begin{aligned}
& n^{1/2}\int_{t_1}^{t}\{\tilde{Y}_x(u) - y_x(u)\}du \\
= \;& n^{1/2}\int_{t_1}^{t}\{\tilde{E}_{yx}(u)(\tilde{E}_{xx}(u))^{-1} - e_{yx}(u)(e_{xx}(u))^{-1}\}du \\
= \;& n^{1/2}\int_{t_1}^{t}\{[\tilde{E}_{yx}(u) - e_{yx}(u)](\tilde{E}_{xx}(u))^{-1} - e_{yx}(u)(\tilde{E}_{xx}(u))^{-1}[\tilde{E}_{xx}(u)
\end{aligned}$$

$$
\begin{aligned}
& -e_{xx}(u)](e_{xx}(u))^{-1}\}du \\
= \; & n^{1/2}\int_{t_1}^{t}\{[\tilde{E}_{yx}(u)-e_{yx}(u)](e_{xx}(u))^{-1}-e_{yx}(u)(e_{xx}(u))^{-1}[\tilde{E}_{xx}(u) \\
& -e_{xx}(u)](e_{xx}(u))^{-1}\}du+o_p(1). \qquad \text{(A.31)}
\end{aligned}
$$

$n^{1/2}\int_{t_1}^{t}\{\tilde{Z}_x(u)-z_x(u)\}du$ has a similar decomposition. Lemma A.2.6 follows from applications of Lemma A.2.5. □

A.3 Proof of Theorems

Proof of Theorem 3.1

By the uniform convergence of $\tilde{Y}_x(t)$ and $\tilde{Z}_x(t)$, which can be proved by using Lemma A.2.3, we have

$$\tilde{\beta}(t;\gamma)=\tilde{Y}_x^T(t)-\tilde{Z}_x^T(t)\gamma \xrightarrow{P} y_x^T(t)-z_x^T(t)\gamma$$

uniformly in $t\in[t_1,t_2]$ as $n\to\infty, h\to 0$. Since $\beta_0(t)=y_x^T(t)-z_x^T(t)\gamma_0$, by using (2.8), replace $\beta(s)$ in (2.3) and Applying Lemma A.2.2 We have $n^{-1}\tilde{l}(\gamma)$ equals

$$
\begin{aligned}
& n^{-1}\sum_{i=1}^{n}R_i\int_0^{\tau}W(s)\{Y_i(s)-(\tilde{Y}_x(s)-\gamma^T\tilde{Z}_x(s))X_i(s)-\gamma^T Z_i(s)\}^2\,dN_i^c(s) \\
& +n^{-1}\sum_{i=1}^{n}(1-R_i)\widehat{E}_S\Big[\int_0^{\tau}W(s)\{Y_i(s)-(\tilde{Y}_x(s)-\gamma^T\tilde{Z}_x(s))X_i(s) \\
& \quad -\gamma^T Z_i(s)\}^2\,dN_i^c(s)\mid\mathcal{X}\Big] \\
= \; & n^{-1}\sum_{i=1}^{n}\ll\int_0^{\tau}W(s)\{Y_i(s)-(\tilde{Y}_x(s)-\gamma^T\tilde{Z}_x(s))X_i(s)-\gamma^T Z_i(s)\}^2\,dN_i^c(s)\gg_R \\
= \; & n^{-1}\sum_{i=1}^{n}\ll\int_0^{\tau}W(s)\{Y_i(s)-\tilde{Y}_x(s)X_i(s)+\gamma^T(\tilde{Z}_x(s)X_i(s) \\
& \quad -Z_i(s))\}^2\,dN_i^c(s)\gg_R
\end{aligned}
$$

where

$$\int_0^{\tau}W(s)\{Y_i(s)-\tilde{Y}_x(s)X_i(s)+\gamma^T(\tilde{Z}_x(s)X_i(s)-Z_i(s))\}^2\,dN_i^c(s)$$

$$
\begin{aligned}
&= \int_0^\tau W(s)[\{Y_i(s) - \tilde{Y}_x(s)X_i(s) + \gamma^T(\tilde{Z}_x(s)X_i(s) - Z_i(s))\}^2 - \{Y_i(s) \\
&\qquad -y_x(s)X_i(s) + \gamma^T(z_x(s)X_i(s) - Z_i(s))\}^2]\, dN_i^c(s) \\
&\quad + \int_0^\tau W(s)\{Y_i(s) - y_x(s)X_i(s) + \gamma^T(z_x(s)X_i(s) - Z_i(s))\}^2\, dN_i^c(s) \\
&= \int_0^\tau \{-(\tilde{Y}_x(s) - y_x(s)) + \gamma^T(\tilde{Z}_x(s) - z_x(s))\}X_i(s)W(s)[2Y_i(s) \\
&\qquad -(\tilde{Y}_x(s) + y_x(s))X_i(s) + \gamma^T\{(\tilde{Z}_x(s) + z_x(s))X_i(s) - 2Z_i(s)\}]dN_i^c(s) \\
&\quad + \int_0^\tau W(s)\{Y_i(s) - y_x(s)X_i(s) + \gamma^T(z_x(s)X_i(s) - Z_i(s))\}^2\, dN_i^c(s) \\
&= \int_0^\tau \{-(\tilde{Y}_x(s) - y_x(s)) + \gamma^T(\tilde{Z}_x(s) - z_x(s))\}X_i(s)W(s)\{-(\tilde{Y}_x(s) - y_x(s))X_i(s) \\
&\qquad +\gamma^T(\tilde{Z}_x(s) - z_x(s))X_i(s) + 2y_x(s)X_i(s) + 2Y_i(s) \\
&\qquad +\gamma^T(2z_x(s)X_i(s) - 2Z_i(s))\}dN_i^c(s) \\
&\quad + \int_0^\tau W(s)\{Y_i(s) - y_x(s)X_i(s) + \gamma^T(z_x(s)X_i(s) - Z_i(s))\}^2\, dN_i^c(s) \\
&= \int_0^\tau [\{-(\tilde{Y}_x(s) - y_x(s)) + \gamma^T(\tilde{Z}_x(s) - z_x(s))\}X_i(s)]^2 W(s) dN_i^c(s) \\
&\quad + \int_0^\tau 2\{-(\tilde{Y}_x(s) - y_x(s)) + \gamma^T(\tilde{Z}_x(s) - z_x(s))\}X_i(s)W(s)\{y_x(s)X_i(s) + Y_i(s) \\
&\qquad +\gamma^T(z_x(s)X_i(s) - Z_i(s))\}dN_i^c(s) \\
&\quad + \int_0^\tau W(s)\{Y_i(s) - y_x(s)X_i(s) + \gamma^T(z_x(s)X_i(s) - Z_i(s))\}^2\, dN_i^c(s)
\end{aligned}
$$

So by the linearity of the operation $\ll \gg_R$,

$$
\begin{aligned}
n^{-1}\tilde{l}(\gamma) &= n^{-1}\sum_{i=1}^n \ll \int_0^\tau [\{-(\tilde{Y}_x(s) - y_x(s)) + \gamma^T(\tilde{Z}_x(s) - z_x(s))\}X_i(s)]^2 W(s) \\
&\qquad dN_i^c(s) \gg_R \\
&\quad + n^{-1}\sum_{i=1}^n \ll \int_0^\tau 2\{-(\tilde{Y}_x(s) - y_x(s)) + \gamma^T(\tilde{Z}_x(s) - z_x(s))\}X_i(s)W(s) \\
&\qquad \{y_x(s)X_i(s) + Y_i(s) + \gamma^T(z_x(s)X_i(s) - Z_i(s))\}dN_i^c(s) \gg_R \\
&\quad + n^{-1}\sum_{i=1}^n \ll \int_0^\tau W(s)\{Y_i(s) - y_x(s)X_i(s) + \gamma^T(z_x(s)X_i(s) - Z_i(s))\}^2 \\
&\qquad dN_i^c(s) \gg_R + o_p(1)
\end{aligned}
$$

The first term equals

$$
\begin{aligned}
& n^{-1}\sum_{i=1}^{n} R_i \int_0^{\tau} [\{-(\tilde{Y}_x(s)-y_x(s))+\gamma^T(\tilde{Z}_x(s)-z_x(s))\}X_i(s)]^2 W(s)dN_i^c(s) \\
& +n^{-1}\sum_{i=1}^{n}(1-R_i)\widehat{E}_s\Big\{\int_0^{\tau}[\{-(\tilde{Y}_x(s)-y_x(s))+\gamma^T(\tilde{Z}_x(s)-z_x(s))\}X_i(s)]^2 W(s) \\
& \quad dN_i^c(s)\mid \mathcal{X}\Big\} \\
= \; & n^{-1}\sum_{i=1}^{n} R_i \int_0^{\tau} [\{-(\tilde{Y}_x(s)-y_x(s))+\gamma^T(\tilde{Z}_x(s)-z_x(s))\}X_i(s)]^2 W(s)dN_i^c(s) \\
& +n^{-1}\sum_{i=1}^{n}(1-R_i)E_s\Big\{\int_0^{\tau}[\{-(\tilde{Y}_x(s)-y_x(s))+\gamma^T(\tilde{Z}_x(s)-z_x(s))\}X_i(s)]^2 W(s) \\
& \quad dN_i^c(s)\mid \mathcal{X}\Big\}+o_p(1) \\
= \; & \int_0^{\tau}\{-(\tilde{Y}_x(s)-y_x(s))+\gamma^T(\tilde{Z}_x(s)-z_x(s))\}\Big(n^{-1}\sum_{i=1}^{n}R_iX_i(s)X_i(s)^TW(s) \\
& \quad dN_i^c(s)\Big)\{-(\tilde{Y}_x(s)-y_x(s))+\gamma^T(\tilde{Z}_x(s)-z_x(s))\}^T \\
& +E_s\Big\{\int_0^{\tau}\{-(\tilde{Y}_x(s)-y_x(s))+\gamma^T(\tilde{Z}_x(s)-z_x(s))\}\Big(n^{-1}\sum_{i=1}^{n}(1-R_i)X_i(s)X_i(s)^T \\
& \quad W(s)dN_i^c(s)\Big)\{-(\tilde{Y}_x(s)-y_x(s))+\gamma^T(\tilde{Z}_x(s)-z_x(s))\}^T\mid \mathcal{X}\Big\}+o_p(1) \\
= \; & \int_0^{\tau}\{-(\tilde{Y}_x(s)-y_x(s))+\gamma^T(\tilde{Z}_x(s)-z_x(s))\}d\Big(n^{-1}\sum_{i=1}^{n}\int_0^{s}R_iX_i(u)X_i(u)^TW_i(u) \\
& \quad dN_i^c(u)\Big)\{-(\tilde{Y}_x(s)-y_x(s))+\gamma^T(\tilde{Z}_x(s)-z_x(s))\}^T \\
& +E_s\Big\{\int_0^{\tau}\{-(\tilde{Y}_x(s)-y_x(s))+\gamma^T(\tilde{Z}_x(s)-z_x(s))\}d\Big(n^{-1}\sum_{i=1}^{n}\int_0^{s}(1-R_i)X_i(u) \\
& \quad X_i(u)^TW(u)dN_i^c(u)\Big)\{-(\tilde{Y}_x(s)-y_x(s))+\gamma^T(\tilde{Z}_x(s)-z_x(s))\}^T\mid \mathcal{X}\Big\} \\
& +o_p(1).
\end{aligned}
$$

Since

$$
n^{-1}\sum_{i=1}^{n}\int_0^{s}R_iX_i(u)X_i(u)^TW(u)dN_i^c(u)
$$

$$\begin{aligned}
&\xrightarrow{P} \quad E\Big\{\int_0^s R_i X_i(u)X_i(u)^T W(u)dN_i^c(u)\Big\}, \\
&\quad\; n^{-1}\sum_{i=1}^n \int_0^s (1-R_i)X_i(u)X_i(u)^T W(u)dN_i^c(u) \\
&\xrightarrow{P} \quad E\Big\{\int_0^s (1-R_i)X_i(u)X_i(u)^T W(u)dN_i^c(u)\Big\}
\end{aligned}$$

and by the uniform convergence of $\tilde{Y}_x(s)$ and $\tilde{Z}_x(s)$ which lead to $-(\tilde{Y}_x(s)-y_x(s))+\gamma^T(\tilde{Z}_x(s)-z_x(s)) \xrightarrow{P} 0$, the first term converges to zero in probability.

The second term equals

$$\begin{aligned}
& n^{-1}\sum_{i=1}^n R_i \int_0^\tau 2\{-(\tilde{Y}_x(s)-y_x(s))+\gamma^T(\tilde{Z}_x(s)-z_x(s))\}X_i(s)W(s)\{y_x(s)X_i(s) \\
&\quad +Y_i(s)+\gamma^T[z_x(s)X_i(s)-Z_i(s)]\}dN_i^c(s) \\
& +n^{-1}\sum_{i=1}^n (1-R_i)\widehat{E}_s\Big\{\int_0^\tau 2\{-(\tilde{Y}_x(s)-y_x(s))+\gamma^T(\tilde{Z}_x(s)-z_x(s))\}X_i(s)W(s) \\
&\quad \{y_x(s)X_i(s)+Y_i(s)+\gamma^T[z_x(s)X_i(s)-Z_i(s)]\}dN_i^c(s) \mid \mathcal{X}\Big\} \\
= \;& \int_0^\tau 2\{-(\tilde{Y}_x(s)-y_x(s))+\gamma^T(\tilde{Z}_x(s)-z_x(s))\}d\Big(n^{-1}\sum_{i=1}^n \int_0^s R_i X_i(u)W(u) \\
&\quad \{y_x(u)X_i(u)+Y_i(u)+\gamma^T[z_x(u)X_i(u)-Z_i(u)]\}dN_i^c(u)\Big) \\
& +E_s\Big\{\int_0^\tau 2\{-(\tilde{Y}_x(s)-y_x(s))+\gamma^T(\tilde{Z}_x(s)-z_x(s))\}d\Big(n^{-1}\sum_{i=1}^n \int_0^s (1-R_i)X_i(u) \\
&\quad W(u)\{y_x(u)X_i(u)+Y_i(u)+\gamma^T[z_x(u)X_i(u)-Z_i(u)]\}dN_i^c(u)\Big) \mid \mathcal{X}\Big\} \\
& +o_p(1).
\end{aligned}$$

Also

$$\begin{aligned}
&\quad\; n^{-1}\sum_{i=1}^n \int_0^s R_i X_i(u)W(u)\{y_x(u)X_i(u)+Y_i(u) \\
&\qquad\qquad +\gamma^T[z_x(u)X_i(u)-Z_i(u)]\}dN_i^c(u) \\
&\xrightarrow{P} \quad E\Big\{\int_0^s R_i X_i(u)W(u)\{y_x(u)X_i(u)+Y_i(u) \\
&\qquad\qquad +\gamma^T[z_x(u)X_i(u)-Z_i(u)]\}dN_i^c(u)\Big\},
\end{aligned}$$

$$n^{-1}\sum_{i=1}^{n}\int_0^s (1-R_i)X_i(u)W(u)\{y_x(u)X_i(u)+Y_i(u)$$
$$+\gamma^T[z_x(u)X_i(u)-Z_i(u)]\}dN_i^c(u)$$
$$\xrightarrow{P} \quad E\bigg\{\int_0^s (1-R_i)X_i(u)W(u)\{y_x(u)X_i(u)+Y_i(u)$$
$$+\gamma^T[z_x(u)X_i(u)-Z_i(u)]\}dN_i^c(u)\bigg\}.$$

Similarly to the first term, the second term converges to zero in probability.

Therefore according to our lemma A.2.2,

$$\begin{aligned}
n^{-1}\tilde{l}(\gamma) &= n^{-1}\sum_{i=1}^{n} \ll \int_0^\tau W(s)\{Y_i(s)-y_x(s)X_i(s)+\gamma^T(z_x(s)X_i(s)\\
&\quad -Z_i(s))\}^2\, dN_i^c(s) \gg_R + o_p(1)\\
&\xrightarrow{P} E\bigg\{\int_0^\tau w(s)\{Y_i(s)-y_x(s)X_i(s)+\gamma^T(z_x(s)X_i(s)-Z_i(s))\}^2\, dN_i^c(s)\bigg\}\\
&= E\bigg\{\int_0^\tau w(s)\{Y_i(s)-(y_x(s)-\gamma_0^T z_x(s))X_i(s)-\gamma_0^T Z_i(s)\\
&\quad +(\gamma-\gamma_0)^T(z_x(s)X_i(s)-Z_i(s))\}^2\, dN_i^c(s)\bigg\}\\
&= E\bigg\{\int_0^\tau w(s)\{\epsilon_i(s)+(\gamma-\gamma_0)^T(z_x(s)X_i(s)-Z_i(s))\}^2\, dN_i^c(s)\bigg\}\\
&= E\bigg\{\int_0^\tau w(s)\{\epsilon_i^2(s)+2\epsilon_i(s)[(\gamma-\gamma_0)^T(z_x(s)X_i(s)-Z_i(s))]\\
&\quad +[(\gamma-\gamma_0)^T(z_x(s)X_i(s)-Z_i(s))]^2\}\, dN_i^c(s)\bigg\}\\
&= E\bigg\{\int_0^\tau w(s)\{\epsilon_i^2(s)+[(\gamma-\gamma_0)^T(z_x(s)X_i(s)-Z_i(s))]^2\}\, dN_i^c(s)\bigg\}\\
&\quad +E\bigg\{\int_0^\tau 2w(s)\epsilon_i(s)(\gamma-\gamma_0)^T(z_x(s)X_i(s)-Z_i(s))dN_i^c(s)\bigg\}\\
&= E\bigg\{\int_0^\tau w(s)\{\epsilon_i^2(s)+[(\gamma-\gamma_0)^T(z_x(s)X_i(s)-Z_i(s))]^2\}\, dN_i^c(s)\bigg\}\\
&\quad +\int_0^\tau E\{E[2w(s)\epsilon_i(s)(\gamma-\gamma_0)^T(z_x(s)X_i(s)-Z_i(s))dN_i^c(s)\mid X_i(s),\\
&\quad Z_i(s)]\}\\
&= E\bigg\{\int_0^\tau w(s)\{\epsilon_i^2(s)+[(\gamma-\gamma_0)^T(z_x(s)X_i(s)-Z_i(s))]^2\}\, dN_i^c(s)\bigg\}\\
&\quad +\int_0^\tau E\{2w(s)(\gamma-\gamma_0)^T(z_x(s)X_i(s)-Z_i(s))E[\epsilon_i(s)dN_i^c(s)\mid X_i(s),
\end{aligned}$$

$$
\begin{aligned}
& \qquad Z_i(s)]\} \\
&= E\Big\{ \int_0^{\tau} w(s)\{\epsilon_i^2(s) + [(\gamma-\gamma_0)^T(z_x(s)X_i(s) - Z_i(s))]^2\}\, dN_i^c(s) \Big\} \\
&\quad + \int_0^{\tau} E\{2w(s)(\gamma-\gamma_0)^T(z_x(s)X_i(s) - Z_i(s))E[\epsilon_i(s) \mid X_i(s), Z_i(s)] \\
&\qquad E[dN_i^c(s) \mid X_i(s), Z_i(s)]\} \\
&= E\Big\{ \int_0^{\tau} w(s)\{\epsilon_i^2(s) + [(\gamma-\gamma_0)^T(z_x(s)X_i(s) - Z_i(s))]^2\}\, dN_i^c(s) \Big\} \\
&\equiv l_0(\gamma) \geq l_0(\gamma_0) \equiv E\Big\{ \int_0^{\tau} w(s)\epsilon_i^2(s) dN_i^c(s) \Big\},
\end{aligned}
$$

uniformly in γ in Γ. Let $d(\gamma, \gamma_0)$ be the Euclidean distance between γ and γ_0. Therefore, for every $\epsilon > 0$,

$$
\begin{aligned}
& \sup_{\gamma: d(\gamma,\gamma_0)\geq\epsilon} (-l_0(\gamma)) = -\inf_{\gamma: d(\gamma,\gamma_0)\geq\epsilon} l_0(\gamma) \\
&= -\inf_{\gamma: d(\gamma,\gamma_0)\geq\epsilon} E\Big\{ \int_0^{\tau} w(s)\{\epsilon_i^2(s) + [(\gamma-\gamma_0)^T(z_x(s)X_i(s) - Z_i(s))]^2\}\, dN_i^c(s) \Big\} \\
&< -\inf_{\gamma: d(\gamma,\gamma_0)\geq\epsilon} E\Big\{ \int_0^{\tau} w(s)\{\epsilon_i^2(s) dN_i^c(s) \Big\} = -\inf_{\gamma: d(\gamma,\gamma_0)\geq\epsilon} l_0(\gamma_0) \\
&= \sup_{\gamma: d(\gamma,\gamma_0)\geq\epsilon} (-l_0(\gamma_0)).
\end{aligned}
$$

Then according to Theorem 5.7 of van der Vaart (1998), we have $\widehat{\gamma} \xrightarrow{P} \gamma_0$. □

Proof of Theorem 3.2

By continuous mapping theorem, the asymptotic uniform consistency of $\widehat{\beta}(t)$ on $[t_1, t_2]$ can be easily obtained by the consistency of $\widehat{\gamma}$, the uniform consistency of $\tilde{Y}_x(t)$ and $\tilde{Z}_x(t)$ since $\widehat{\beta}(t) = \tilde{Y}_x^T(t) - \tilde{Z}_x^T(t)\widehat{\gamma}$. □

Proof of Theorem 3.3

Recall the score function $U(\gamma)$ and the Taylor expansion of $U(\widehat{\gamma})$ at γ_0

$$
n^{1/2}(\widehat{\gamma} - \gamma_0) = -\left(n^{-1} \frac{\partial U(\gamma^*)}{\partial \gamma^T} \right)^{-1} [n^{-1/2} U(\gamma_0)], \tag{A.32}
$$

where γ^* is on the line segment between $\widehat{\gamma}$ and γ_0.

By plugging (2.8) into the score function (2.9) we will have

$$\begin{aligned} U(\gamma) &= \sum_{i=1}^{n} \int_{t_1}^{t_2} \ll W(t)\{Z_i(t) - \tilde{Z}_x(t)X_i(t)\}\{Y_i(t) - X_i^T(t)(\tilde{Y}_x^T(t) \\ &\quad -\tilde{Z}_x^T(t)\gamma) - Z_i^T(t)\gamma\}\, dN_i^c(t) \gg_R \\ &= \sum_{i=1}^{n} \int_{t_1}^{t_2} \ll W(t)\{Z_i(t) - \tilde{Z}_x(t)X_i(t)\}\{Y_i(t) - X_i^T(t)\tilde{Y}_x^T(t) + (X_i^T(t)\tilde{Z}_x^T(t) \\ &\quad -Z_i^T(t))\gamma\}\, dN_i^c(t) \gg_R . \end{aligned}$$

Then take the partial derivative with respect to γ, we get

$$n^{-1}\frac{\partial U(\gamma^*)}{\partial \gamma^T} = -n^{-1}\sum_{i=1}^{n}\int_{t_1}^{t_2} \ll W(t)\{Z_i(t) - \tilde{Z}_x(t)X_i(t)\}^{\otimes 2}\, dN_i^c(t) \gg_R . \tag{A.33}$$

According to the similar argument we discussed in the proof of consistency of $\widehat{\gamma}$, $\tilde{Z}_x(t)$ and $W(t)$ can be replaced by their limits $z_x(t)$ and $w(t)$ respectively, and this change only contributes a $o_p(1)$ difference to the above equation. Thus by Lemma A.2.2

$$\begin{aligned} n^{-1}\frac{\partial U(\gamma^*)}{\partial \gamma^T} &= -n^{-1}\sum_{i=1}^{n} \ll \int_{t_1}^{t_2} w(t)\{Z_i(t) - z_x(t)X_i(t)\}^{\otimes 2}\, dN_i^c(t) \gg_R + o_p(1) \\ &\xrightarrow{P} -E\bigg(\int_{t_1}^{t_2} w(t)\{Z_i(t) - z_x(t)X_i(t)\}^{\otimes 2}\, dN_i^c(t)\bigg) = -D. \end{aligned} \tag{A.34}$$

Now we define $\mathcal{B}(t) = \int_{t_1}^{t} \beta_0(s)ds$ and a mean zero process

$$M_i(t; \mathcal{B}, \gamma, \alpha) = \int_{t_1}^{t} \{[Y_i(s) - \gamma^T Z_i(s)]dN_i^c(s) - \xi_i(s)\alpha_i(s)X_i^T(s)d\mathcal{B}(s)\}. \tag{A.35}$$

For simplicity, we use $M_i(t) = M_i(t; \mathcal{B}, \gamma_0, \alpha)$. Also let $O_i(t) = N_i^c(t) - \int_0^t \xi_i(s)\alpha_i(s)ds$. Let $\epsilon_i(t) = Y_i(t) - X_i^T(t)\beta_0(t) - Z_i^T(t)\gamma_0$. Then

$$\begin{aligned} &dM_i(t) - \beta_0^T(t)X_i(t)dO_i(t) \\ &= [Y_i(t) - \gamma_0^T Z_i(t)]dN_i^c(t) - \xi_i(t)\alpha_i(t)X_i^T(t)d\mathcal{B}(t) - \beta_0^T(t)X_i(t)dN_i^c(t) \\ &\quad +\beta_0^T(t)X_i(t)\xi_i(t)\alpha_i(t)dt \\ &= [Y_i(t) - \gamma_0^T Z_i(t) - \beta_0^T(t)X_i(t)]dN_i^c(t) - \xi_i(t)\alpha_i(t)X_i^T(t)\beta_0(t)d(t) \\ &\quad +\beta_0^T(t)X_i(t)\xi_i(t)\alpha_i(t)dt \end{aligned}$$

$$= \epsilon_i(t) dN_i^c(t), \tag{A.36}$$

It follows that

$$\begin{aligned} n^{-1/2}U(\gamma_0) &= n^{-1/2}\sum_{i=1}^{n}\int_{t_1}^{t_2} \ll W(t)\{Z_i(t) - \tilde{Z}_x(t)X_i(t)\}\{Y_i(t) - X_i^T(t)\tilde{\beta}(t;\gamma_0) \\ &\quad -Z_i^T(t)\gamma_0\}\, dN_i^c(t) \gg_R \\ &= n^{-1/2}\sum_{i=1}^{n}\int_{t_1}^{t_2} \ll W(t)\{Z_i(t) - \tilde{Z}_x(t)X_i(t)\}\epsilon_i(t)\, dN_i^c(t) \gg_R \\ &\quad -n^{-1/2}\sum_{i=1}^{n}\int_{t_1}^{t_2} \ll W(t)\{Z_i(t) - \tilde{Z}_x(t)X_i(t)\}X_i^T(t)\{\tilde{\beta}(t;\gamma_0) - \beta_0(t)\} \\ &\quad dN_i^c(t) \gg_R \end{aligned}$$

Denote the second term by η. Next we show that $\eta \xrightarrow{P} 0$. We have

$$\begin{aligned} \eta &= n^{-1/2}\sum_{i=1}^{n}\int_{t_1}^{t_2} \ll W(t)\{Z_i(t) - z_x(t)X_i(t)\}X_i^T(t)\{\tilde{\beta}(t;\gamma_0) - \beta_0(t)\}\, dN_i^c(t) \gg_R \\ &\quad -n^{-1/2}\sum_{i=1}^{n}\int_{t_1}^{t_2} \ll W(t)\{\tilde{Z}_x(t) - z_x(t)\}X_i(t)X_i^T(t)\{\tilde{\beta}(t;\gamma_0) - \beta_0(t)\} \\ &\quad dN_i^c(t) \gg_R . \end{aligned} \tag{A.37}$$

The two terms in (A.37) are denoted as η_1 and η_2 repectively. Then the first term

$$\begin{aligned} \eta_1 &= n^{-1/2}\int_{t_1}^{t_2} W(t) \ll \sum_{i=1}^{n} Z_i(t)X_i^T(t)\, dN_i^c(t) \gg_R \{\tilde{\beta}(t;\gamma_0) - \beta_0(t)\} \\ &\quad -n^{-1/2}\int_{t_1}^{t_2} W(t) \ll \sum_{i=1}^{n} z_x(t)X_i(t)X_i^T(t)\, dN_i^c(t) \gg_R \{\tilde{\beta}(t;\gamma_0) - \beta_0(t)\} \\ &= n^{-1/2}\int_{t_1}^{t_2} W(t) d\Big(\int_{t_1}^{t} \ll \sum_{i=1}^{n} Z_i(u)X_i^T(u)\, dN_i^c(u) \gg_R \Big)\{\tilde{\beta}(t;\gamma_0) - \beta_0(t)\} \\ &\quad -n^{-1/2}\int_{t_1}^{t_2} W(t) d\Big(\int_{t_1}^{t} \ll \sum_{i=1}^{n} z_x(u)X_i(u)X_i^T(u)\, dN_i^c(u) \gg_R \Big)\{\tilde{\beta}(t;\gamma_0) - \beta_0(t)\}. \end{aligned} \tag{A.38}$$

By Lemma A.2.2, we have

$$n^{-1}\sum_{i=1}^{n}\int_{t_1}^{t} \ll Z_i(u)X_i^T(u)\, dN_i^c(u) \gg_R \xrightarrow{P} E\Big(\int_{t_1}^{t} Z_i(u)X_i^T(u)\, dN_i^c(u)\Big)$$

$$= E\Big(\int_{t_1}^{t} \xi_i(u)\alpha_i(u)Z_i(u)X_i^T(u)du\Big) = \int_{t_1}^{t} e_{zx}(u)du,$$

and

$$\begin{aligned} & n^{-1}\sum_{i=1}^{n}\int_{t_1}^{t} \ll z_x(u)X_i(u)X_i^T(u)\,dN_i^c(u) \gg_R \\ \xrightarrow{P} \; & E\Big(\int_{t_1}^{t} z_x(u)X_i(u)X_i^T(u)\,dN_i^c(u)\Big) = E\Big(\int_{t_1}^{t} z_x(u)\xi_i(u)\alpha_i(u)X_i(u)X_i^T(u)du\Big) \\ = \; & \int_{t_1}^{t} z_x(u)e_{xx}(u)du = \int_{t_1}^{t} e_{zx}(u)du. \end{aligned}$$

Therefore, $\int_{t_1}^{t} \ll Z_i(u)X_i^T(u)\,dN_i^c(u) \gg_R$ and $\int_{t_1}^{t} \ll z_x(u)X_i(u)X_i^T(u)\,dN_i^c(u) \gg_R$ achieve the same mean. Based on (A.38), we have

$$\begin{aligned} \eta_1 = \; & \int_{t_1}^{t_2} W(t)d\Big\{n^{1/2}\Big(n^{-1}\sum_{i=1}^{n}\int_{t_1}^{t} \ll Z_i(u)X_i^T(u)\,dN_i^c(u) \gg_R - \int_{t_1}^{t} e_{zx}(u)du\Big)\Big\} \\ & \{\tilde\beta(t;\gamma_0) - \beta_0(t)\} \\ & - \int_{t_1}^{t_2} W(t)d\Big\{n^{1/2}\Big(n^{-1}\sum_{i=1}^{n}\int_{t_1}^{t} \ll z_x(u)X_i(u)X_i^T(u)\,dN_i^c(u) \gg_R \\ & - \int_{t_1}^{t} e_{zx}(u)du\Big)\Big\}\{\tilde\beta(t;\gamma_0) - \beta_0(t)\}. \end{aligned} \tag{A.39}$$

Hence $\eta_1 \xrightarrow{P} 0$ follows from the weak convergence of

$$n^{1/2}\Big(n^{-1}\sum_{i=1}^{n}\int_{t_1}^{t} \ll Z_i(u)X_i^T(u)\,dN_i^c(u) \gg_R - \int_{t_1}^{t} e_{zx}(u)du\Big)$$

and

$$n^{1/2}\Big(n^{-1}\sum_{i=1}^{n}\int_{t_1}^{t} \ll z_x(u)X_i(u)X_i^T(u)\,dN_i^c(u) \gg_R - \int_{t_1}^{t} e_{zx}(u)du\Big),$$

also the application of consistency of $\tilde\beta(t;\gamma_0)$ and Lemma 1 of Lin & Ying (2001).

The second term of (A.37)

$$\begin{aligned} \eta_2 = \; & n^{-1/2}\int_{t_1}^{t_2} \{\tilde Z_x(t) - z_x(t)\}W(t)\sum_{i=1}^{n} \ll X_i(t)X_i^T(t)\,dN_i^c(t) \gg_R \{\tilde\beta(t;\gamma_0) \\ & -\beta_0(t)\} \end{aligned}$$

$$= \quad n^{-1/2}\int_{t_1}^{t_2} W(t)\{\tilde{Z}_x(t) - z_x(t)\} d\Big(\int_{t_1}^{t}\sum_{i=1}^{n} \ll X_i(u)X_i^T(u)\, dN_i^c(u) \gg_R\Big)$$
$$\{\tilde{\beta}(t;\gamma_0) - \beta_0(t)\}.$$

Using similar arguments of deriving (A.39), $\eta_2 \xrightarrow{P} 0$. Therefore, $\eta = \eta_1 + \eta_2 \xrightarrow{P} 0$. Hence

$$\begin{aligned} n^{-1/2}U(\gamma_0) &= n^{-1/2}\sum_{i=1}^{n}\int_{t_1}^{t_2} \ll W(t)\{Z_i(t) - \tilde{Z}_x(t)X_i(t)\}\epsilon_i(t)dN_i^c(t) \gg_R + o_p(1) \\ &= n^{-1/2}\sum_{i=1}^{n}\int_{t_1}^{t_2} \ll W(t)\{Z_i(t) - z_x(t)X_i(t)\}\epsilon_i(t)dN_i^c(t) \gg_R \\ &\quad - n^{-1/2}\int_{t_1}^{t_2} W(t)\{\tilde{Z}_x(t) - z_x(t)\} d\Big(\sum_{i=1}^{n}\int_{t_1}^{t} \ll X_i(u)\epsilon_i(u)dN_i^c(u) \gg_R\Big) \\ &\quad + o_p(1). \end{aligned} \tag{A.40}$$

The second term of (A.40) converges to 0 in probability by using integration by parts, lemma A.2.2, Lemma A.2.6 and Lemma A.1 of Lin & Ying (2001). The first term of (A.40) is

$$\begin{aligned} &n^{-1/2}\sum_{i=1}^{n}\int_{t_1}^{t_2} R_i\{W(t)\{Z_i(t) - z_x(t)X_i(t)\}\epsilon_i(t)dN_i^c(t) \\ &+ n^{-1/2}\sum_{i=1}^{n}\int_{t_1}^{t_2}(1-R_i)\widehat{E}_s\{W(t)\{Z_i(t) - z_x(t)X_i(t)\}\epsilon_i(t)dN_i^c(t) \mid \mathcal{X}\} + o_p(1). \end{aligned} \tag{A.41}$$

The second term of (A.41) is

$$\begin{aligned} &n^{-1/2}\sum_{i=1}^{n}\int_{t_1}^{t_2}(1-R_i)E_s\{w(t)\{Z_i(t) - z_x(t)X_i(t)\}\epsilon_i(t)dN_i^c(t) \mid \mathcal{D}_i, R_i = 0\} \\ &+ n^{-1/2}\sum_{i=1}^{n}\int_{t_1}^{t_2}(1-R_i)\widehat{E}_s\{w(t)\{Z_i(t) - z_x(t)X_i(t)\}\epsilon_i(t)dN_i^c(t) \mid \mathcal{D}_i, R_i = 0\} \\ &- n^{-1/2}\sum_{i=1}^{n}\int_{t_1}^{t_2}(1-R_i)E_s\{w(t)\{Z_i(t) - z_x(t)X_i(t)\}\epsilon_i(t)dN_i^c(t) \mid \mathcal{D}_i, R_i = 0\} \\ &+ o_p(1) \end{aligned}$$

$$\begin{aligned}
&= n^{-1/2}\sum_{i=1}^{n}\int_{t_1}^{t_2}(1-R_i)E_s\{w(t)\{Z_i(t)-z_x(t)X_i(t)\}\epsilon_i(t)dN_i^c(t)\mid\mathcal{D}_i,R_i=0\} \\
&\quad +n^{-1/2}\sum_{i=1}^{n}(1-R_i)\int_0^L\sum_{j=1}^{n_i}I(t_1\le s+T_{ij}\le t_2)w(s+T_{ij})\{Z_{ij} \\
&\qquad -z_x(s+T_{ij})X_{ij}\}\epsilon_i(s+T_{ij})I(C_i\ge T_{ij})\left[\frac{d\widehat{F}_s(s)}{\widehat{F}_s(V_i)}-\frac{dF_s(s)}{F_s(V_i)}\right] \qquad (A.42) \\
&\qquad +o_p(1)
\end{aligned}$$

Write

$$\frac{d\widehat{F}_s(s)}{\widehat{F}_s(V_i)}-\frac{dF_s(s)}{F_s(V_i)}=\frac{d\{\widehat{F}_s(s)-F_s(s)\}}{\widehat{F}_s(V_i)}+\left\{\frac{1}{\widehat{F}_s(V_i)}-\frac{1}{F_s(V_i)}\right\}dF_s(s),$$

and

$$J_i(s)=\sum_{j=1}^{n_i}I(t_1\le s+T_{ij}\le t_2)W(s+T_{ij})\{Z_{ij}-z_x(s+T_{ij})X_{ij}\}\epsilon_i(s+T_{ij})I(C_i\ge T_{ij}).$$

The second term of (A.42) is

$$\begin{aligned}
& n^{-1/2}\sum_{i=1}^{n}(1-R_i)\int_0^L J_i(s)(\widehat{F}_s(V_i))^{-1}d\{\widehat{F}_s(s)-F_s(s)\} \\
+ \; & n^{-1/2}\sum_{i=1}^{n}(1-R_i)\int_0^L J_i(s)\{(\widehat{F}_s(V_i))^{-1}-(F_s(V_i))^{-1}\}dF_s(s) \qquad (A.43)
\end{aligned}$$

Since $n^{-1}\sum_{i=1}^{n}(1-R_i)J_i(s)(\widehat{F}_s(V_i))^{-1}\xrightarrow{P}E\{(1-R_i)J_i(s)(\widehat{F}_s(V_i))^{-1}\}=0$ uniformly in $s\in[0,L]$, and $n^{-1/2}(\widehat{F}_s(s)-F_s(s))$ converges weakly on $[0,L]$, we have the first term of (A.43) converges to zero in probability. By the decomposition (A.1), it also follows that the second term of (A.43) is

$$n^{-1}\sum_{i=1}^{n}(1-R_i)\int_0^L J_i(s)(F_s(V_i))^{-1}n^{1/2}\{F_s(V_i)-\widehat{F}_s(V_i)\}dF_s(s)+o_p(1)\xrightarrow{P}0.$$

Hence by (A.40), (A.41), (A.42) and (A.43), we have

$$n^{-1/2}U(\gamma_0) = n^{-1/2}\sum_{i=1}^{n}\int_{t_1}^{t_2}R_iw(t)\{Z_i(t)-z_x(t)X_i(t)\}\epsilon_i(t)dN_i^c(t)$$

$$+n^{-1/2}\sum_{i=1}^{n}\int_{t_1}^{t_2}(1-R_i)E_s[w(t)\{Z_i(t)-z_x(t)X_i(t)\}\epsilon_i(t)dN_i^c(t)\mid \mathcal{D}_i,$$
$$R_i=0]+o_p(1). \qquad (A.44)$$

By (A.32), (A.34) and (A.44), we have

$$n^{1/2}(\widehat{\gamma}-\gamma_0)=D^{-1}[n^{-1/2}U(\gamma_0)]+o_p(1).$$

Hence $n^{1/2}(\widehat{\gamma}-\gamma_0)\xrightarrow{D}\mathcal{N}(0,D^{-1}VD^{-1})$. □

Let $\tilde{e}_{yx}(t)=\int_0^\tau K_h(u-t)e_{yx}(u)du$. Similar definitions can be defined for $\tilde{e}_{zx}(t)$ and $\tilde{e}_{xx}(t)$. Let $\beta^*(t)=\tilde{y}_x^T(t)-\tilde{z}_x^T(t)\gamma_0$, where $\tilde{y}_x(t)=\tilde{e}_{yx}(t)(\tilde{e}_{xx}(t))^{-1}$ and $\tilde{z}_x(t)=\tilde{e}_{zx}(t)(\tilde{e}_{xx}(t))^{-1}$. We have the fact that $\tilde{e}_{yx}(t)=\int_0^\tau K_h(u-t)e_{yx}(u)du\xrightarrow{P}e_{yx}(u)$ as $h\to 0$. Similar facts hold for $\tilde{e}_{xx}(t)$ and $\tilde{e}_{zx}(t)$ too. The transpose of the matrix is denoted by changing the order of the subscripts. And $e'_{yx}(t)$ and $e''_{yx}(t)$ are the first and second derivatives of $e_{yx}(t)$, respectively.

Proof of Theorem 3.4

Since $\widehat{\beta}(t)=\tilde{\beta}(t;\widehat{\gamma})=\tilde{Y}_x^T-\tilde{Z}_x^T\widehat{\gamma}$ and $\beta^*(t)=\tilde{y}_x^T(t)-\tilde{z}_x^T(t)\gamma_0$, applying Taylor expansion for $\widehat{\beta}(t)=\tilde{\beta}(t,\widehat{\gamma})$ at γ_0, also noting that $n^{1/2}(\widehat{\gamma}-\gamma_0)\xrightarrow{D}\mathcal{N}(0,D^{-1}VD^{-1})$ and

$$\frac{\partial\tilde{\beta}(t;\gamma_0)}{\partial\gamma}=-\tilde{Z}_x(t)\xrightarrow{P}-z_x(t),$$

we have

$$\begin{aligned}
&(nh)^{1/2}(\widehat{\beta}(t)-\beta^*(t))\\
=\;&(nh)^{1/2}(\tilde{\beta}(t;\gamma_0)-\beta^*(t))-(nh)^{1/2}(\widehat{\gamma}-\gamma_0)\tilde{Z}_x(t)\\
=\;&(nh)^{1/2}(\tilde{\beta}(t;\gamma_0)-\beta^*(t))+O_p(h^{1/2}). \qquad (A.45)
\end{aligned}$$

By the weak convergence of $(nh)^{1/2}\{\tilde{E}_{yx}(t)-\tilde{e}_{yx}(t)\}$, $(nh)^{1/2}\{\tilde{E}_{zx}(t)-\tilde{e}_{zx}(t)\}$ and $(nh)^{1/2}\{\tilde{E}_{xx}(t)-\tilde{e}_{xx}(t)\}$, and the convergence of $\tilde{E}_{xx}(t)$ from Lemma A.2.3, we have

$$
\begin{aligned}
& \tilde{\beta}(t;\gamma_0) - \beta^*(t) \\
= \;& \tilde{Y}_x^T(t) - \tilde{Z}_x^T(t)\gamma_0 - \{\tilde{y}_x^T(t) - \tilde{z}_x^T(t)\gamma_0\} \\
= \;& (\tilde{E}_{xx}(t))^{-1}\tilde{E}_{xy}(t) - (\tilde{E}_{xx}(t))^{-1}\tilde{E}_{xz}(t)\gamma_0 - (\tilde{e}_{xx}(t))^{-1}\tilde{e}_{xy}(t) + (\tilde{e}_{xx}(t))^{-1}\tilde{e}_{xz}(t)\gamma_0 \\
= \;& (\tilde{E}_{xx}(t))^{-1}[\{\tilde{E}_{xy}(t) - \tilde{e}_{xy}(t)\} - \{\tilde{E}_{xz}(t) - \tilde{e}_{xz}(t)\}\gamma_0] \\
& -(\tilde{e}_{xx}(t))^{-1}\{\tilde{E}_{xx}(t) - \tilde{e}_{xx}(t)\}(\tilde{E}_{xx}(t))^{-1}\{\tilde{e}_{xy}(t) - \tilde{e}_{xz}(t)\gamma_0\} \\
= \;& (e_{xx}(t))^{-1}[\{\tilde{E}_{xy}(t) - \tilde{e}_{xy}(t)\} - \{\tilde{E}_{xz}(t) - \tilde{e}_{xz}(t)\}\gamma_0] \\
& -(e_{xx}(t))^{-1}\{\tilde{E}_{xx}(t) - \tilde{e}_{xx}(t)\}\beta_0(t) + o_p((nh)^{-1/2}) \\
= \;& (e_{xx}(t))^{-1}[(\tilde{E}_{xy}(t) - \tilde{e}_{xy}(t)) - (\tilde{E}_{xz}(t) - \tilde{e}_{xz}(t))\gamma_0 - (\tilde{E}_{xx}(t) - \tilde{e}_{xx}(t))\beta_0(t)] \\
& + o_p((nh)^{-1/2}). \qquad \text{(A.46)}
\end{aligned}
$$

Let

$$
\begin{aligned}
\phi_1(t) &= n^{-1}\sum_{i=1}^n \int_0^t R_i X_i(u) X_i^T(u) dN_i^c(u), \\
\phi_2(t) &= n^{-1}\sum_{i=1}^n \int_0^t (1-R_i) X_i(u) X_i^T(u) dN_i^c(u), \\
\theta_1(t) &= E\{R_i X_i(t) X_i^T(t)\xi_i(t)\alpha_i(t)\}, \\
\theta_2(t) &= E\{(1-R_i) X_i(t) X_i^T(t)\xi_i(t)\alpha_i(t)\}.
\end{aligned}
$$

Note that

$$
\begin{aligned}
& \int_0^\tau K_h(u-t) E\{\xi_i(u)\alpha_i(u) X_i(u)\epsilon_i(u)\} du \\
= \;& \int_0^\tau K_h(u-t) E\{\xi_i(u)\alpha_i(u) X_i(u) E[\epsilon_i(u) \mid X_i(u), Z_i(u), \xi_i(u)]\} du = 0.
\end{aligned}
$$

We have

$$
\begin{aligned}
& (nh)^{1/2}(\tilde{\beta}(t;\gamma_0) - \beta^*(t)) \\
= \;& (nh)^{1/2}(e_{xx}(t))^{-1}\Big(n^{-1}\sum_{i=1}^n R_i \int_0^\tau K_h(u-t) X_i(u)[Y_i(u) - Z_i^T(u)\gamma_0
\end{aligned}
$$

$$
\begin{aligned}
& -X_i^T(u)\beta_0(u)]dN_i^c(u) \\
& +n^{-1}\sum_{i=1}^n (1-R_i)\widehat{E}_s\Big\{\int_0^\tau K_h(u-t)X_i(u)[Y_i(u)-Z_i^T(u)\gamma_0 \\
& -X_i^T(u)\beta_0(u)]dN_i^c(u) \mid \mathcal{X}\Big\} \\
& -\int_0^\tau K_h(u-t)E\{\xi_i(u)\alpha_i(u)X_i(u)[Y_i(u)-Z_i^T(u)\gamma_0 \\
& -X_i^T(u)\beta_0(u)]\}du\Big) \\
& -(nh)^{1/2}(e_{xx}(t))^{-1}\Big(n^{-1}\sum_{i=1}^n R_i\int_0^\tau K_h(u-t)X_i(u)X_i^T(u)[\beta_0(t)-\beta_0(u)]dN_i^c(u) \\
& +n^{-1}\sum_{i=1}^n (1-R_i)\widehat{E}_s\Big\{\int_0^\tau K_h(u-t)X_i(u)X_i^T(u)[\beta_0(t)-\beta_0(u)] \\
& dN_i^c(u) \mid \mathcal{X}\Big\} \\
& -\int_0^\tau K_h(u-t)E\{\xi_(u)\alpha_i(u)X_i(u)X_i^T(u)\}[\beta_0(t)-\beta_0(u)]du\Big) \\
& +o_p((nh)^{-1/2}) \\
= \; & (nh)^{1/2}(e_{xx}(t))^{-1}\Big[n^{-1}\sum_{i=1}^n R_i\int_0^\tau K_h(u-t)X_i(u)\epsilon_i(u)dN_i^c(u) \\
& +n^{-1}\sum_{i=1}^n (1-R_i)\widehat{E}_s\Big\{\int_0^\tau K_h(u-t)X_i(u)\epsilon_i(u)dN_i^c(u) \mid \mathcal{X}\Big\}\Big] \\
& -(nh)^{1/2}(e_{xx}(t))^{-1}\Big(\int_0^\tau K_h(u-t)d\phi_1(u)(\beta_0(t)-\beta_0(u)) \\
& +\widehat{E}_s\Big\{\int_0^\tau K_h(u-t)d\phi_2(u)(\beta_0(t)-\beta_0(u)) \mid \mathcal{X}\Big\} \\
& -\int_0^\tau K_h(u-t)E\{\xi_(u)\alpha_i(u)X_i(u)X_i^T(u)\}[\beta_0(t)-\beta_0(u)]du\Big) \\
& +o_p((nh)^{-1/2}). \qquad \text{(A.47)}
\end{aligned}
$$

The third term of (A.47) is

$$
\begin{aligned}
& (nh)^{1/2}\int_0^\tau K_h(u-t)d\phi_1(u)(\beta_0(t)-\beta_0(u)) \\
= \; & (nh)^{1/2}\int_0^\tau K_h(u-t)d\{E(\phi_1(u))\}(\beta_0(t)-\beta_0(u)) \\
& +h^{1/2}\int_0^\tau K_h(u-t)n^{1/2}d\{\phi_1(u)-E(\phi_1(u))\}(\beta_0(t)-\beta_0(u))
\end{aligned}
$$

$$
\begin{aligned}
&= (nh)^{1/2}\int_0^\tau K_h(u-t)\theta_1(u)(\beta_0(t)-\beta_0(u))du + o_p(1) \\
&= \mu_2(nh^5)^{1/2}((1/2)\theta_1(t)\beta_0''(t)+\theta_1'(t)\beta_0'(t)) + o_p((nh^5)^{1/2}) + o_p(h^{1/2}), \quad \text{(A.48)}
\end{aligned}
$$

where the second equality holds since $n^{1/2}\{\phi_1(u) - E(\phi_1(u))\}$ converges weakly and $h^{1/2}K_h(u-t)(\beta_0(t)-\beta_0(u)) \to 0$ as $h \to 0$ and $n \to \infty$, and the third equality hold by applying Taylor Expansions at t. Similarly,

$$
\begin{aligned}
&(nh)^{1/2}\int_0^\tau K_h(u-t)d\phi_2(u)(\beta_0(t)-\beta_0(u)) \\
= \; & -\mu_2(nh^5)^{1/2}((1/2)\theta_2(t)\beta_0''(t)+\theta_2'(t)\beta_0'(t)) + o_p((nh^5)^{1/2}) + o_p(h^{1/2}). \quad \text{(A.49)}
\end{aligned}
$$

Futher,

$$
\begin{aligned}
&\int_0^\tau (nh)^{1/2}K_h(u-t)E\{\xi_(u)\alpha_i(u)X_i(u)X_i^T(u)\}[\beta_0(t)-\beta_0(u)]du \\
= \; & -\mu_2(nh^5)^{1/2}[e_{xx}'(t)\beta_0'(t)+(1/2)e_{xx}(t)\beta_0''(t)] + o_p((nh^5)^{1/2}). \quad \text{(A.50)}
\end{aligned}
$$

Hence,

$$
(A.48) + (A.49) - (A.50) = o_p((nh^5)^{1/2}). \quad \text{(A.51)}
$$

It follows that from (A.47),

$$
\begin{aligned}
&(nh)^{1/2}(\tilde\beta(t;\gamma_0)-\beta^*(t)) \\
= \; & (nh)^{1/2}(e_{xx}(t))^{-1}\Bigg(n^{-1}\sum_{i=1}^n \ll \int_0^\tau K_h(u-t)X_i(u)\epsilon_i(u)dN_i^c(u) \gg_R \Bigg) \\
& + o_p((nh^5)^{1/2}) \quad \text{(A.52)} \\
= \; & (nh)^{1/2}(e_{xx}(t))^{-1}\Bigg(n^{-1}\sum_{i=1}^n R_i\int_0^\tau K_h(u-t)X_i(u)\epsilon_i(u)dN_i^c(u) \\
& + n^{-1}\sum_{i=1}^n(1-R_i)\widehat{E}_s\bigg\{\int_0^\tau K_h(u-t)X_i(u)\epsilon_i(u)dN_i^c(u) \mid \mathcal{X}_i\bigg\}\Bigg) + o_p((nh^5)^{1/2}) \\
= \; & (nh)^{1/2}(e_{xx}(t))^{-1}\Bigg(n^{-1}\sum_{i=1}^n R_i\int_0^\tau K_h(u-t)X_i(u)\epsilon_i(u)dN_i^c(u) \\
& + n^{-1}\sum_{i=1}^n(1-R_i)E_s\bigg\{\int_0^\tau K_h(u-t)X_i(u)\epsilon_i(u)dN_i^c(u) \mid \mathcal{D}_i, R_i=0\bigg\}
\end{aligned}
$$

$$
\begin{aligned}
&+n^{-1}\sum_{i=1}^{n}(1-R_i)\widehat{E}_s\Big\{\int_0^\tau K_h(u-t)X_i(u)\epsilon_i(u)dN_i^c(u)\mid \mathcal{D}_i, R_i=0\Big\}\\
&-n^{-1}\sum_{i=1}^{n}(1-R_i)E_s\Big\{\int_0^\tau K_h(u-t)X_i(u)\epsilon_i(u)dN_i^c(u)\mid \mathcal{D}_i, R_i=0\Big\}\Big)\\
&+o_p((nh^5)^{1/2}). \qquad (A.53)
\end{aligned}
$$

By (A.47), (A.51) and Lemma A.2.4, it follows that

$$
\begin{aligned}
& (nh)^{1/2}(\tilde{\beta}(t;\gamma_0)-\beta^*(t))\\
= \; & (nh)^{1/2}(e_{xx}(t))^{-1}\Big(n^{-1}\sum_{i=1}^{n}R_i\int_0^\tau K_h(u-t)X_i(u)\epsilon_i(u)dN_i^c(u)\\
& +n^{-1}\sum_{i=1}^{n}(1-R_i)E_s\Big\{\int_0^\tau K_h(u-t)X_i(u)\epsilon_i(u)dN_i^c(u)\mid \mathcal{D}_i, R_i=0\Big\}\Big)\\
& +o_p(h^{1/2}). \qquad (A.54)
\end{aligned}
$$

Let

$$
\begin{aligned}
\delta_n(t) &= n^{-1/2}\sum_{i=1}^{n}\int_0^t R_iX_i(u)\epsilon_i(u)dN_i^c(u)\\
&\quad +n^{-1/2}\sum_{i=1}^{n}\int_0^t(1-R_i)X_i(u)\epsilon_i(u)E(dN_i^c(u)\mid \mathcal{D}_i, R_i=0)\\
&= n^{-1/2}\sum_{i=1}^{n}\int_0^t X_i(u)\epsilon_i(u)d\{R_iN_i^c(u)+(1-R_i)E(N_i^c(u)\mid \mathcal{D}_i, R_i=0)\}\\
&= n^{-1/2}\sum_{i=1}^{n}\int_0^t X_i(u)\epsilon_i(u)dN_i^R(u).
\end{aligned}
$$

Then $\delta_n(t)\xrightarrow{D}\delta(t)$, a mean zero Gaussian process. We can write

$$
(nh)^{1/2}(\tilde{\beta}(t;\gamma_0)-\beta^*(t)) = h^{1/2}(e_{xx}(t))^{-1}\int_0^\tau K_h(u-t)d\delta_n(t)+o_p(h^{1/2}). \qquad (A.55)
$$

Remind the definition of $N_i^R(u)$ introduced in Chapter 3,

$$
\begin{aligned}
\delta_n(t) &= n^{-1/2}\sum_{i=1}^{n}\int_0^t X_i(u)\epsilon_i(u)dN_i^R(u)\\
&= n^{-1/2}\sum_{i=1}^{n}\int_0^t X_i(u)\epsilon_i(u)dM_i^R(u)+n^{-1/2}\sum_{i=1}^{n}\int_0^t X_i(u)\epsilon_i(u)\alpha_i^R(u)du.
\end{aligned}
$$

(A.56)

Note that

$$
\begin{aligned}
& E\{X_i(u)\epsilon_i(u)\alpha_i^R(u)du\} \\
= \; & E[X_i(u)\epsilon_i(u)E\{dN_i^R(u) \mid \mathcal{F}_{u-}^R\}] = E\{X_i(u)\epsilon_i(u)dN_i^R(u)\} \\
= \; & E\{X_i(u)\epsilon_i(u)R_i dN_i^c(u)\} + E\{X_i(u)\epsilon_i(u)(1-R_i)E(dN_i^c(u) \mid \mathcal{D}_i, R_i = 0)\} \\
= \; & E\{X_i(u)\epsilon_i(u)R_i dN_i^c(u)\} + E\{X_i(u)\epsilon_i(u)(1-R_i)dN_i^c(u)\} \\
= \; & E\{X_i(u)\epsilon_i(u)dN_i^c(u)\} = 0.
\end{aligned}
$$

The second term of (A.56) converges weakly to a mean zero Gaussian process. Hence

$$
\begin{aligned}
& h^{1/2}\int_0^\tau K_h(u-t)n^{-1/2}\sum_{i=1}^n X_i(u)\epsilon_i(u)\alpha_i^R(u)du \\
= \; & h^{1/2}\int_0^\tau K_h(u-t)d\Big(n^{-1/2}\sum_{i=1}^n\int_0^u X_i(w)\epsilon_i(w)\alpha_i^R(w)dw\Big) \qquad \text{(A.57)}
\end{aligned}
$$

Let $\zeta_n(u) = n^{-1/2}\sum_{i=1}^n\int_0^u X_i(w)\epsilon_i(w)\alpha_i^R(w)dw$. Then $\zeta_n(u) \xrightarrow{D} \zeta(u)$, a Gaussian process. By the almost sure representation theorem (Shorack & Wellner, 1986), there exist $\zeta_n^*(u)$ and $\zeta^*(u)$ on same probability space that have the same distributions and sample paths as $\zeta_n(u)$ and $\zeta(u)$, respectively, such that $\sup_{u\in[0,\tau]}|\,\zeta_n^*(u) - \zeta^*(u)| = O_p(n^{-1/2+\alpha})$ for $\alpha > 0$. Hence (A.57) equals

$$
\begin{aligned}
& h^{1/2}\int_0^\tau K_h(u-t)d\zeta_n(u) \overset{D}{=} h^{1/2}\int_0^\tau K_h(u-t)d\zeta_n^*(u) \\
= \; & h^{1/2}\int_0^\tau K_h(u-t)d(\zeta_n^*(u) - \zeta^*(u)) + h^{1/2}\int_0^\tau K_h(u-t)d\zeta^*(u). \qquad \text{(A.58)}
\end{aligned}
$$

By integration by parts and

$$
\begin{aligned}
& h^{1/2}\int_{t-h}^{t+h}(\zeta_n^*(u) - \zeta^*(u))h^{-1}dK((u-t)/h) \\
= \; & h^{1/2}\int_{t-h}^{t+h}(\zeta_n^*(u) - \zeta^*(u))h^{-2}K'((u-t)/h)du \\
\leq \; & h^{-1/2}n^{-1/2+\alpha}\sup_{u\in[0,\tau]} n^{1/2-\alpha}|\,\zeta_n^*(u) - \zeta^*(u)|
\end{aligned}
$$

$$= O_p((nh)^{-1/2}n^{\alpha}) = o_p(1).$$

The last equality holds for $0 < \alpha < 1/4$ and $nh^2 \to \infty$, the first term of (A.58) is of the order of $o_p(1)$. And the second term of (A.58) is $h^{1/2}\zeta^*(t) = O(h^{1/2})$. Then $(A.57) \xrightarrow{P} 0$. By (A.55), (A.56) and $(A.57) \xrightarrow{P} 0$, we have

$$\begin{aligned}
& (nh)^{1/2}(\tilde{\beta}(t;\gamma_0) - \beta^*(t)) \\
= \; & h^{1/2}(e_{xx}(t))^{-1}\int_0^{\tau} K_h(u-t)d\Big\{n^{-1/2}\sum_{i=1}^{n}\int_0^{u} X_i(w)\epsilon_i(w)dM_i^R(w)\Big\} \\
& +o_p(1). \qquad \text{(A.59)}
\end{aligned}$$

The first term of (A.59) is a martingale in τ with respect to $\mathcal{F}_{\tau}^R$, with the predictable variation process equal to

$$\begin{aligned}
& h(e_{xx}(t))^{-1}\int_0^{\tau} K_h^2(u-t)n^{-1}\sum_{i=1}^{n} X_i(u)X_i^T(u)\epsilon_i^2(u)\alpha_i^R(u)du(e_{xx}(t))^{-1} \\
\to \; & \mu_0(e_{xx}(t))^{-1}E\{X_i(t)X_i^T(t)\epsilon_i^2(t)\alpha_i^R(t)\}(e_{xx}(t))^{-1} = \mu_0\Sigma(t).
\end{aligned}$$

Now note that

$$\begin{aligned}
\tilde{e}_{xy}(t) &= \int_0^{\tau} K_h(s-t)e_{xy}(s)ds = \int_{t-h}^{t+h} h^{-1}K(\frac{s-t}{h})e_{xy}(s)ds \\
&= \int_{-1}^{1} K(x)e_{xy}(t+xh)dx \\
&= \int_{-1}^{1} K(x)(e_{xy}(t) + hxe'_{xy}(t) + (1/2)h^2x^2e''_{xy}(t) + o(h^2))dx \\
&= e_{xy}(t)\int_{-1}^{1} K(x)dx + he'_{xy}(t)\int_{-1}^{1} xK(x)dx + (1/2)h^2e''_{xy}(t)\int_{-1}^{1} x^2K(x)dx \\
&\quad +o(h^2) \\
&= e_{xy}(t) + (1/2)\mu_2h^2e''_{xy}(t) + o(h^2).
\end{aligned}$$

Similar results hold for $\tilde{e}_{xx}(t)$ and $\tilde{e}_{xz}(t)$. Following some tedious calculations, we have

$$\tilde{y}_x^T(t) = (\tilde{e}_{xx}(t))^{-1}\tilde{e}_{xy}(t)$$

$$
\begin{aligned}
&= (e_{xx}(t) + (1/2)\mu_2 h^2 e''_{xx}(t) + o(h^2))^{-1}(e_{xy}(t) + (1/2)\mu_2 h^2 e''_{xy}(t) + o(h^2)) \\
&= y_x^T(t) + (1/2)\mu_2 h^2 (e_{xx}(t))^{-1}[e''_{xy}(t) - e''_{xx}(t)(e_{xx}(t))^{-1} e_{xy}(t)] + o(h^2),
\end{aligned}
$$

and

$$
\tilde{z}_x^T(t) = z_x^T(t) + (1/2)\mu_2 h^2 (e_{xx}(t))^{-1}[e''_{xz}(t) - e''_{xx}(t)(e_{xx}(t))^{-1} e_{xz}(t)] + o(h^2).
$$

Thus

$$
\begin{aligned}
\beta^*(t) &= \tilde{y}_x^T(t) - \tilde{z}_x^T(t)\gamma_0 \\
&= y_x^T(t) - z_x^T(t)\gamma_0 + (1/2)\mu_2 h^2 (e_{xx}(t))^{-1}[e''_{xy}(t) - e''_{xx}(t)(e_{xx}(t))^{-1} e_{xy}(t)] \\
&\quad -(1/2)\mu_2 h^2 (e_{xx}(t))^{-1}[e''_{xz}(t) - e''_{xx}(t)(e_{xx}(t))^{-1} e_{xz}(t)]\gamma_0 + o(h^2) \\
&= y_x^T(t) - z_x^T(t)\gamma_0 + (1/2)\mu_2 h^2 (e_{xx}(t))^{-1}[e''_{xy}(t) - e''_{xx}(t) y_x^T(t)] \\
&\quad -(1/2)\mu_2 h^2 (e_{xx}(t))^{-1}[e''_{xz}(t) - e''_{xx}(t) z_x^T(t)]\gamma_0 + o(h^2) \\
&= \beta_0(t) + (1/2)\mu_2 h^2 (e_{xx}(t))^{-1}[e''_{xy}(t) - e''_{xz}(t)\gamma_0 - e''_{xx}(t)\beta_0(t)] + o(h^2) \\
&= \beta_0(t) + \beta_{Bias}(t) + o(h^2). \qquad \text{(A.60)}
\end{aligned}
$$

Therefore,

$$
(nh)^{1/2}(\widehat{\beta}(t) - \beta_0(t) - \beta_{Bias}(t)) \xrightarrow{D} \mathcal{N}(0, \mu_0 \Sigma(t)),
$$

as $n \to \infty$, $h \to 0$, $nh^2 \to \infty$, $nh^5 = O(1)$. □