Cox regression analysis for distorted covariates with an unknown distortion function

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Abstract

We study inference for censored survival data where some covariates are distorted by some unknown functions of an observable confounding variable in a multiplicative form. Example of this kind of data in medical studies is the common practice to normalizing some important observed exposure variables by patients’ body mass index (BMI), weight or age. Such phenomenon also appears frequently in environmental studies where ambient measure is used for normalization, and in genomic studies where library size needs to be normalized for next generation sequencing data. We propose a new covariate-adjusted Cox proportional hazards regression model and utilize the kernel smoothing method to estimate the distorting function, then employ an estimated maximum likelihood method to derive estimator for the regression parameters. We establish the large sample properties of the proposed estimator. Extensive simulation studies demonstrate that the proposed estimator performs well in correcting the bias arising from distortion. A real data set from the National Wilms’ Tumor Study (NWTS) is used to illustrate the proposed approach.

Keywords: Bandwidth selection, Covariate adjustment, Cox regression model, Distorting function, Estimated maximum likelihood method, Multiplicative effect

1. Introduction

In real studies, the primary covariates sometimes are not directly recorded in their true values, but rather, they are observed in a distorted form, where the distortion is in the form of a multiplicative factor. This type of data does not get sufficient attention as other types of covariate measurement error problems, even though they are also quite wide prevalent in real studies. For example, when releasing household data on energy use, in order to maintain confidentiality, the U.S. Department of Energy multiplied the survey data by some randomly selected numbers before publication (Hwang, 1986). Therefore, the contaminated data available to the public is $\tilde{X} = X \cdot U$, where $X$ and $U$ respectively denote the true data and the randomly selected number. This multiplicative contamination structure is also very common in biomedical studies, in the form of normalization, as some primary covariates are often normalised by a confounder such as BMI ($BMI = \text{weight}/\text{height}^2$) or by other measures of body configuration or age. For instance, in

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a study of the relationship between the fibrinogen level (FIB) and serum transferrin level (TRF) among hemodialysis patients, Kaysen et al. (2002) found that BMI has a great influence on FIB and TRF and may distort the true relationship between them. Therefore, they proposed a calibration method where dividing the observed FIB and TRF by the confounding variable BMI. This implies a multiplicative structure between the unobserved primary variables and the confounding variable. Such phenomenon also appears frequently in environmental studies where ambient measure is used for normalization, and in genomic studies where library size needs to be normalized for next generation sequencing data.

In some situations, however, the precise nature of multiplicative relationship between the primary variables and the confounding variable could be unknown, and in this case the naive practice of dividing by the confounding variable may result in biased estimates or losing of power for statistical inference. To overcome these difficulties, Sentürk & Müller (2005) considered a more flexible multiplicative form which is an unknown function of the confounding variable $U$. They proposed a covariate adjustment method for the linear regression model, where both the response ($Y$) and the covariates ($X$) are distorted by an observable confounder $U$, i.e., $\tilde{X} = \phi(U)X$, $\tilde{Y} = \varphi(U)Y$, where $\tilde{X}$ and $\tilde{Y}$ are observable distorted covariates and response, $\phi(\cdot)$ and $\varphi(\cdot)$ are unknown smooth distorting functions. Directly applying the widely used ordinary least squares (OLS) method to the contaminated data $(\tilde{X}, \tilde{Y})$ will result in biased and inconsistent estimates. Sentürk & Müller (2005) corrected the bias by linking it to a varying-coefficient regression model, then utilized the bin method (Fan & Zhang, 2000) to obtain consistent estimators (Sentürk & Müller, 2006). Related research includes Nguyen & Sentürk (2008) on generalizing this method to the case of multiple distorting covariates, Sentürk & Müller (2009) on extending to generalized linear model, Zhang, Zhu, & Liang (2012) and Zhang et al. (2013) on the nonlinear regression model and the partial linear model. More recently, Cui et al. (2009) developed a direct plug-in estimation procedure for nonlinear regression model with one confounding variable. They proposed to estimate the distorting functions $\varphi(\cdot)$ and $\phi(\cdot)$ by nonparametrically regressing the response and predictors on the distorting variable, and obtained the estimates $(\hat{X}, \hat{Y})$ for the unobservable response and predictors, then conducted the nonlinear least squares method on the estimated counterparts $(\hat{X}, \hat{Y})$. Zhang, Zhu, & Zhu (2012) further applied this direct plug-in method to semiparametric model by incorporating dimension reduction techniques. To relax the parametric assumptions and some restrictive conditions on distorting functions in the existing literature, Delaigle, Hall, & Zhou (2016) proposed a more flexible nonparametric estimator for the regression function.

In this paper, we focus on investigating censored survival data where the response of interest is a right-censored survival time and the primary predictor $X$ is distorted by an observable confounding variable $U$ through the multiplicative form $\tilde{X} = \phi(U)X$, where $\phi(\cdot)$ is the unknown distorted function. A reasonable identifiability condition for this structure is $E[\phi(U)] = 1$ corresponding to the assumption that the mean distorting effect vanishes (Sentürk & Müller, 2005). The existing methods mentioned earlier can not be applicable here due to censoring. Furthermore, the existing methods for censored survival data with mismeasured covariates (e.g., Prentice, 1982; Wang et al., 1997; Zhou & Pepe, 1995; Zhou & Wang, 2000; Huang & Wang, 2000; Hu & Lin, 2002) can not handle this multiplicative distortion. To make valid inference, we propose a covariate-adjusted Cox proportional hazards regression to address this
multiplicative contamination structure. Inspired by Cui et al. (2009), we first employ the nonparametric regression to obtain consistent estimator of the distorting function $\phi(\cdot)$ through the kernel smoothing method, and obtain the estimates for the true covariates $X$ by $\hat{X} = \tilde{X}/\hat{\phi}(U)$. Then the regression parameters are estimated by maximizing the partial likelihood on the estimated data. Our approach has several distinctive advantages. First, the contamination structure we considered is more general which includes a large class of confounding mechanisms, e.g., $\phi(\cdot) = 1$ means there is no contamination, $\phi(U) = U$ represents the contamination structure $\tilde{X} = X \cdot U$. So the applicability of our proposed method can be quite broad. Second, the computation of our method is simple and fast, which will greatly facilitates its implementation in real application.

The rest of the article is organized as follows. In Section 2, we introduce the covariate-adjust Cox regression for the multiplicative contaminated data and present the proposed covariate-calibration method. In Section 3, we establish the asymptotic properties of the proposed estimates. In Section 4, we present simulation results to evaluate the finite sample performance of the proposed estimates. In Section 5, we apply the proposed method to a data set from the National Wilms’ Tumor Study (NWTS). Some concluding remarks are given in Section 6. All technical proofs are presented in the supplementary material.

2. Cox regression with multiplicative contamination structure

2.1. Model, data and contamination structure

To fix notation, let $T$ denote the survival time, $C$ denote the censoring time, $\tilde{T} = \min(T, C)$ denote the observed time, and $\Delta = I(T \leq C)$ denote the failure indicator. Let $Z = (Z_1, Z_2, \ldots, Z_p)^T$ and $X$ be the associated covariates where $X$ is the one that subjects to multiplicative contamination. Assume that the censoring mechanism is random, that is, the survival time $T$ and the censoring time $C$ are conditionally independent given $Z$ and $X$. The proportional hazards regression model (Cox, 1972) assumes that the conditional hazard function of the survival time $T$ associated with covariates $Z$ and $X$ takes the form of

$$
\lambda(t|Z, X) = \lambda_0(t) \exp(\beta^T Z + \gamma X),
$$

where $\lambda_0(t)$ is the baseline hazard function, $\beta = (\beta_1, \beta_2, \ldots, \beta_p)^T$ and $\gamma$ are the unknown regression coefficients. We assume the scalar covariate $X$ is not observed precisely while the $p$-dimensional covariate $Z$ could be accurately observed. Assume the observed data consists of $n$ subjects, denoted by $(\tilde{T}_i, \Delta_i, Z_i, U_i, \tilde{X}_i), i = 1, \ldots, n$, which are independent samples from $(\tilde{T}, \Delta, Z, U, \tilde{X})$. Instead of exact $X_i$, we observe $\tilde{X}_i$ such that

$$
\tilde{X}_i = \phi(U_i)X_i,
$$

where $U_i$ is an observable variable and independent of $X_i$, $\phi(\cdot)$ is an unknown link function. To make the model identifiability, we assume that $E\{\phi(U_i)\} = 1$, which implies that the distorting effect vanishes on average.
We aim to infer the regression parameters $\beta$ and $\gamma$ based on the observations available. When $X_i$ are observed without contamination, maximizing the partial likelihood (Cox, 1975)

$$L_n(\beta, \gamma) = \prod_{i=1}^{n} \left\{ \frac{\exp(\beta^T Z_i + \gamma X_i)}{\sum_{j=1}^{n} I(T_j > T_i) \exp(\beta^T Z_j + \gamma X_j)} \right\}^{\Delta_i}$$

(2)
can offer the estimates for $\beta$ and $\gamma$. It is evident that (2) can not be used when $X_i$ are unobservable or contaminated.

Note that the established methods on the Cox regression with additive contamination structure $\tilde{X} = X + U$ always require error $U$ to be independent of $X$ (e.g., Huang & Wang, 2000; Li & Ryan, 2004). Directly apply the additive error structure methods to current setting is not feasible. To illustrate this, even though the multiplicative contamination structure (1) can also be rewritten as an additive structure, $\tilde{X} = X + X \{\phi(U) - 1\}$, (3)
or

$$\log \tilde{X} = \log X + \log \{\phi(U)\},$$

(4)
the error $X \{\phi(U) - 1\}$ is not independent of $X$, hence the methods mentioned above can not be applicable here. If one takes the logarithmic transformation assuming the related quantities are positive, then one would arrive at the additive covariate contamination structure (4). Here the error term $\log \{\phi(U)\}$ is independent of $\log X$, but extra variation needs to be accounted for in the back-transformation procedure. Moreover, the routine approximately corrected score method for the Cox regression at the scale $\log X$ would result in biased estimate if the correct Cox regression model is linear in $X$.

2.2. Covariate-calibration method

Our proposed approach is based on directly calibrating $X_i$. Note that

$$\phi(u) = \frac{E(\tilde{X} | U = u)}{E(X)} = \frac{E(\tilde{X} | U = u)}{E(X)}.$$

We can employ the commonly used Nadaraya–Watson kernel smoothing estimate for $\psi(u) = E(\tilde{X} | U = u)$, which is given by

$$\hat{\psi}(u) = \frac{\sum_{i=1}^{n} K \{(u - U_i)/h_n\} \tilde{X}_i}{\sum_{i=1}^{n} K \{(u - U_i)/h_n\}},$$

where $K(\cdot)$ is the kernel smoothing function and $h_n$ is the bandwidth. Since $\tilde{X}_n = n^{-1} \sum_{i=1}^{n} \tilde{X}_i$ converges to $E(\tilde{X})$ almost surely by using the strong law of large numbers, we can obtain an consistent estimate for $\phi(u)$ as $\hat{\phi}(u) = \hat{\psi}(u)/\tilde{X}_n$. Following (4), we propose a calibration of $X_i$ by $\tilde{X}_i = \tilde{X}_i / \hat{\phi}(U_i)$. Therefore, we can construct an estimated partial likelihood using $\tilde{X}_i$ as follows,

$$\hat{L}_n(\beta, \gamma) = \prod_{i=1}^{n} \left\{ \frac{\exp(\beta^T Z_i + \gamma \tilde{X}_i)}{\sum_{j=1}^{n} I(T_j > T_i) \exp(\beta^T Z_j + \gamma \tilde{X}_j)} \right\}^{\Delta_i}.$$

(5)
The proposed estimator $(\hat{\beta}, \hat{\gamma})$ was defined as the maximizer for $\hat{L}_n(\beta, \gamma)$, i.e.,

$$(\hat{\beta}, \hat{\gamma}) = \arg \max_{(\beta, \gamma)} \hat{L}_n(\beta, \gamma).$$

(6)
2.3. Bandwidth selection

In real data analysis, it is desirable to have an automatically data-driven method for selecting the bandwidth parameter $h_n$. We will employ a cross-validation (CV) method to choose the optimal $h_n$. The kernel estimate of the density function of $U(p(u))$, is denoted as

$$
\hat{p}(u) = \frac{1}{n h_n} \sum_{i=1}^{n} K \left( \frac{u - U_i}{h_n} \right).
$$

Following Rudemo (1982) and Bowman (1984), we define an integrated squared error (ISE) as follows,

$$
\text{ISE}(h_n) = \int \{\hat{p}(u) - p(u)\}^2 du
= \int \{\hat{p}(u)\}^2 du - 2 \int \hat{p}(u)p(u)du + \int \{p(u)\}^2 du.
$$

As the third term of (7) is free of $h_n$, the minimizer of the ISE($h_n$) is the same as the minimizer of the sum of the first two terms of (7). Let $\hat{p}_{(-i)}(\cdot)$ be the leave-one-out kernel density estimator, i.e.,

$$
\hat{p}_{(-i)}(u) = \frac{1}{n h_n} \sum_{j \neq i}^{n} K \left( \frac{u - U_j}{h_n} \right).
$$

The second term of (7) can be consistently estimated by $-2n^{-1} \sum_{i=1}^{n} \hat{p}_{(-i)}(U_i)$. Therefore, we propose a cross-validation criterion as follows,

$$
\text{CV}(h_n) = \int \{\hat{p}(u)\}^2 du - 2n^{-1} \sum_{i=1}^{n} \hat{p}_{(-i)}(U_i).
$$

Denote

$$
\hat{h}_{n,\text{opt}} = \arg\min_{h_n} \text{CV}(h_n),
$$

which is considered as the optimal bandwidth parameter.

3. Asymptotic properties

We set $\boldsymbol{\theta} = (\beta^T, \gamma)^T$, let $\hat{\boldsymbol{\theta}} = (\hat{\beta}^T, \hat{\gamma})^T$ and $\theta_0 = (\beta_0^T, \gamma_0)^T$ respectively represent the estimation and the true value of the regression parameter $\boldsymbol{\theta}$. The following theorem gives the consistency and asymptotic normality of the proposed estimator $\hat{\boldsymbol{\theta}}$ when $n \to \infty$. The regularity conditions and the proofs of this theorem are given in the Appendixes A and B, respectively.

**Theorem 1.** Let $\hat{\boldsymbol{\theta}} = (\hat{\beta}^T, \hat{\gamma})^T$ be defined by (6). If conditions C1-C9 in the Appendix A are satisfied, the following results hold:

(i) $\hat{\boldsymbol{\theta}}$ covers in probability to the true value $\theta_0$,

(ii) $\sqrt{n}(\hat{\boldsymbol{\theta}} - \theta_0) \overset{d}{\rightarrow} N(0, \Sigma^{-1}(\Sigma + \Omega)\Sigma^{-1})$. 


where $\Sigma = \begin{pmatrix} \Sigma_{11} & \Sigma_{12} \\ \Sigma_{21} & \Sigma_{22} \end{pmatrix}$ is defined in condition $C_4$, $\Sigma_{11}$ denotes the $p$th order sequential principal minor of $\Sigma$, $\zeta = (-\Sigma_{12}^\gamma, 0, -\Sigma_{22}^\gamma)^T$, $\Omega = \frac{\operatorname{Var}(\hat{X}) - \operatorname{Var}(X)}{\{E(X)\}^2} \zeta \zeta^T$.

The above theorem establishes the asymptotic normality of the proposed estimator $\hat{\theta}$, furthermore, from (ii) in Theorem 1, we can obtain the asymptotic distribution of $\hat{\beta}$ and $\hat{\gamma}$ respectively, i.e., $\sqrt{n}(\hat{\beta} - \beta_0) \overset{d}{\to} N(0, (\Sigma^{-1})_p)$ and $\sqrt{n}(\hat{\gamma} - \gamma_0) \overset{d}{\to} N\left(0, (\Sigma^{-1})_{(p+1,p+1)} + \frac{\operatorname{Var}(\hat{X}) - \operatorname{Var}(X)}{\{E(X)\}^2} \gamma_0^2\right)$, where $(\Sigma^{-1})_p$ and $(\Sigma^{-1})_{(p+1,p+1)}$ respectively denote the $p$th order sequential principal minor and the $(p + 1)$th diagonal element of matrix $\Sigma^{-1}$. We note a few remarks on the terms in the expression for the asymptotic covariance matrix. If there is no distortion with $\phi(\cdot) = 1$, we can estimate $\theta$ by maximizing the partial likelihood \cite{2}, the asymptotic covariance matrix of $\hat{\theta}$ is $\Sigma^{-1}$. So the term $\Sigma^{-1} \Omega \Sigma^{-1}$ is caused by the distortion. Furthermore, the limiting variance for $\hat{\gamma}$ includes some unknown components to be estimated, therefore, we can use the sandwich method and plug-in estimation to obtain the standard error and construct the confidence region for $\hat{\gamma}$.

4. Simulation studies

We conducted extensive simulations to investigate the finite-sample performance of the proposed estimator $(\hat{\beta}_p, \hat{\gamma}_p)$ and compared it with two competing estimators. The first one is the naive estimator $(\hat{\beta}_N, \hat{\gamma}_N)$ that ignores the contamination and directly uses $\hat{X}$ to replace $X$; the second one is the oracle estimate $(\hat{\beta}_O, \hat{\gamma}_O)$, which is obtained by assuming that $X$ was known.

The survival times $T_i$ were generated from the Cox proportional hazards model with the conditional hazard function given by

$$\lambda(t | Z_i, X_i) = \lambda_0(t) \exp(\beta_0^T Z_i + \gamma_0 X_i).$$

Set $\beta_0 = (1, 0.5)^T$, $\gamma_0 = 1.5$ and the baseline hazard function $\lambda_0(t) = 1$. The covariate $Z_i = (Z_{i1}, Z_{i2})^T$ follows a multivariate normal distribution with mean 0 and correlation matrix $\Sigma = (0.8|j-k|)$ for $j, k = 1, 2$. We generated $X_i$ from $N(1, 0.5^2)$ and the confounding covariates $U_i$ from a uniform distribution over interval $[2, 6]$. We considered two forms of distortion function $\phi(u) = (u + 3)/7$ and $\phi(u) = 3(u + 1)^2/79$, which satisfy $E\{\phi(U_i)\} = 1$. We took the censoring time $C = \tilde{C} \wedge \tau$, where $\tilde{C}$ was generated from Unif(0, $\tau + 2$). The study duration $\tau$ was chosen to yield the desirable censoring rate. To estimate the disturbing function, we chose Gaussian kernel function $K(t) = \exp(-t^2/2)/\sqrt{2\pi}$ and adopted the leave-one-out cross-validation method to select the bandwidth. We took the sample size $n = 100$ and $n = 200$, coupled with the censoring rates (CR) of 20%, 40% and 80%. For each configuration, we repeated 1000 simulations.

Tables 1 and 2 summarize the results of $(\hat{\beta}_p, \hat{\gamma}_p)$, $(\hat{\beta}_N, \hat{\gamma}_N)$ and $(\hat{\beta}_O, \hat{\gamma}_O)$ under different distortion functions and different censoring rates for sample size $n = 100$ and $n = 200$, respectively. We make the following observations: (i) As expected, in terms of the mean-square error or the coverage probability, the oracle estimator $(\hat{\beta}_O, \hat{\gamma}_O)$ and our proposed estimator $(\hat{\beta}_p, \hat{\gamma}_p)$ are all superior to the naive estimator $(\hat{\beta}_N, \hat{\gamma}_N)$, especially for the results of $\hat{\gamma}$. Not surprisingly, the naive estimator $(\hat{\beta}_N, \hat{\gamma}_N)$ are seriously
biased. For example, under the censoring rate of 20% and \( \phi(u) = 3(u+1)^2/79 \) in Table 1, the bias for \( \hat{\gamma}_N \) is \(-0.810\), more than half of its real value 1.5, while the bias for proposed estimator \( \hat{\gamma}_p \) is only \(-0.047\); moreover, the coverage probability for \( \hat{\gamma}_N \) is 0.006, almost equals to zero. (ii) The proposed estimator \((\hat{\beta}_p, \hat{\gamma}_p)\) are essentially unbiased and comparable with the oracle estimator under different settings, even for the cases with high censoring rate of 80%. For example, in the case of censoring rate= 40% and \( \phi(u) = 3(u+1)^2/79 \) in Table 1, the relative efficiency \( \frac{SD(\hat{\gamma}_p)}{SD(\hat{\gamma}_O)} = 0.341/0.324 = 1.05 \), very close to 1. (iii) Our proposed method performs stably with the choice of the distortion function, while the naive method performs worse if we chose \( \phi(u) = 3(u+1)^2/79 \). The coverage probabilities of \( \hat{\gamma}_N \) for \( \phi(u) = 3(u+1)^2/79 \) almost equal or close to zero. These simulation results demonstrate that the proposed covariate-calibration approach can effectively overcome the negative effect arising from the covariate contamination and meanwhile exhibits good performance.

5. Analysis with Wilms’ tumor study

We applied the proposed covariate-calibration method to the Wilms’ tumor data, which was collected in two randomized studies in Wilms’ tumor patients. Wilms’ tumor is a rare kidney cancer occurring in young children. The National Wilms’ Tumor Study Group (NWTSG) conducted several randomized studies to test different treatments in Wilms’ tumor patients. We use a Wilms’ tumor data including 3915 patients participating in two of the NWTSG trials NWTS-3 and NWTS-4 (D’Angio et al., 1989; Green et al., 1998) to evaluate the joint effect of tumor weight, histological type and other risk factors. The primary endpoint of the study was the survival time (in years). During the follow-up, 444 patients died of Wilms’ tumor and the other 3471 patients were censored, which led to the censoring rate of 88.66%. The mean observed time was 10.33 years (ranging from 0.01 to 22.50 years). We divided the data into two groups according to the histological type (favorable and unfavorable) and summarized the size and mean of each covariate in Table 3. It can be seen that 3476 patients have favorable tumor and the other 439 patients have unfavorable tumor. The mean observed time for patients with favorable tumor is 10.68 years, which is larger then the corresponding value (7.55) of the unfavorable tumor group. Figure 1 shows the Kaplan-Meier curves for the two different tumor histological types, from which we can see that patients with favorable tumor experienced longer survival time.

The predictors included in this analysis are the weight of tumor bearing specimen (abbreviated as wgt, in kilograms), the histological type of the tumor (type, being 0 if favorable and 1 otherwise), tumor stage (stage, coded by 1 and 0, indicating spread of the tumor from localized to metastatic), age at diagnosis (age, measured in years), the study number (num, 1 denotes NWTS-3 and 0 denotes NWTS-4).

We examine the following Cox proportional hazards regression model,

\[
\lambda(t) = \lambda_0(t) \exp(\gamma \cdot \text{wgt} + \beta_1 \cdot \text{type} + \beta_2 \cdot \text{stage} + \beta_3 \cdot \text{age} + \beta_4 \cdot \text{num}).
\]

It is known that the weight of tumor bearing specimen (wgt) is affected by tumor’s diameter (diam, in centimeters). The scatter points of wgt versus diam shown in Figure 2 clearly demonstrate that there indeed exists a strong positive correlation between them. Therefore, we directly adjust for the potential distorting covariate with the proposed method and assume the distortion model as \( \tilde{\text{wgt}} = \phi(\text{diam}) \cdot \text{wgt}, \)
where $\phi(\cdot)$ is an unknown link function, $\text{wgt}$ is the observed wgt. The analysis results of the covariate effects were summarized in Table 4. As a comparison, we also presented the results of the naive method which ignoring the contamination of wgt. By observing the results, the $p$-value of wgt is 0.008 for our proposed method, which means wgt has significant influence on patients’ survival time, while the corresponding value is 0.244 for the naive method without the potential distorting effect of “diam”. From the medical standpoint, wgt has great influence on patients’ survival time, whereas ignoring the contamination leads to this covariate insignificant. Furthermore, from all these two methods, we can conclude that patients with favorable tumor would possess longer survival time, compared with ones with unfavorable tumor, which coincides with Figure 1. As a result, we conclude that the proposed covariate-calibration method offers a convincing result for the Wilms’ tumor data.

6. Conclusion

Covariate-adjusted problem is a common contamination problem in biomedical studies. Similar issues arrive in other field, e.g. in environmental studies, exposures are often calibrated by the daily environment or ambient measures, like the role of BMI in medical studies, or genomic studies where library size is being normalized. Our method deals with the type of some primary covariates that are observed after being distorted by a multiplicative factor (an unknown function of an observable confounding variable). We fill in the gap in the literature on censored survival data with distorting function in primary risk factor, which is lacking in terms of statistical method. We propose a direct estimation procedure to estimate the regression parameters in the Cox proportional hazards regression model. The novel idea of our procedure is to obtain a consistent estimator of the distorted covariate by employing the kernel smoothing method and then obtain the parameter estimation by plugging in the estimated covariate.

Numerical results show that the proposed method is working very well in correcting the bias arising from covariate distortion. It performs stably to a variety choice of the distortion functions. An important improvement of our method is that we allow flexible distorting model to handle various confounding mechanisms. The proposed method is easy to compute and will provide a critical tool for researchers facing with this type data in practice.

A few remarks on using the proposed method in real studies. First, on the construction of confidence interval of the proposed estimation, we note that because of the nonlinear structure of the estimated partial likelihood and the maximum partial likelihood estimation does not have a closed form, the establishment of theoretic properties in this paper is more difficult than linear model. The asymptotic covariance matrix derived in Theorem 1 depends on several unknown components, therefore, it is difficult to construct confidence region based on normal approximation. We recommend to use the common sandwich approach to obtain the standard error estimation. This method has been tested and demonstrated to perform well in our numerical studies.

Second, for ease of exposition, we consider only one confounding variable. In many applications, however, there are multiple distorting variables that simultaneously affect the primary covariate. In principle, the proposed method can handle this case and the sandwich method can be employed as well.
to obtain the standard error estimation. Deriving theoretic properties of the corresponding estimators will be more difficult and need additional technicalities.

Finally, as we require division of the distorted variable by the estimated distorting function, we imposed some regularity assumptions on the curve of the distorting function. In particular, the proposed method can not be applied if $E(X)$ vanishes. Delaigle, Hall, & Zhou (2016) proposed a more flexible nonparametric estimator for the regression function, which significantly weakens some of the strong assumptions on the distorting function. Further research is underway to extend this work to censored survival data.

7. Supplementary materials

The supplementary material presents the detailed proof of Theorem 1.

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Appendix A: Regularity conditions

Unless otherwise stated, all limits are taken as $n \to \infty$. Suppose $a = (a_1, \ldots, a_p)^T$ and $b = (b_1, \ldots, b_p)^T$ are $p$-vectors, then we write $a \otimes b$ for the matrix $ab^T$. Also we write $a^{\otimes 2}$ for the matrix $a \otimes a$. For a matrix $A$ or vector $a$, let $\|A\| = \sup_{i,j} |a_{ij}|$ and $\|a\| = \sup_i |a_i|$. For matrix or vector sequences $A_n$ and $B_n$, denote $A_n \overset{P}{\to} A$ if $\|A_n - A\|_P \to 0$ and denote $A_n = B_n + o_p(1)$ if $\|A_n - B_n\|_P \to 0$. Denote $|a| = (\sum a_i^2)^{1/2}$ and diag($a$) as the diagonal matrix whose diagonal vector is $a$. We set $\theta = (\beta^T, \gamma)^T$, $V = (Z^T, X)^T$, $N_i(t) = I(T_i \leq t, \Delta_i = 1)$, $\bar{N} = \sum_{i=1}^n N_i$, and $Y_i(t) = I(T_i \geq t)$. Let $\tau$ denote the end time of the study. Here, we introduce the following notations:

$$S^{(l)}(\theta, t) = \frac{1}{n} \sum_{i=1}^n V_i^{\otimes l} Y_i(t) \exp \left( V_i^T \theta \right),$$

$$E(\theta, t) = \frac{S^{(1)}(\theta, t)}{S^{(0)}(\theta, t)},$$

$$V(\theta, t) = \frac{S^{(2)}(\theta, t)}{S^{(0)}(\theta, t)} - E(\theta, t)^{\otimes 2},$$

for $l = 0, 1, 2$. Note that $S^{(0)}(\theta, t)$ is a scalar, $S^{(1)}(\theta, t)$ and $E(\theta, t)$ are $(p + 1)$-vectors, $S^{(2)}(\theta, t)$ and $V(\theta, t)$ are $(p + 1) \times (p + 1)$ matrices. Before proving the theorem, we first describe the regular conditions needed as follows:

C1. (Finite interval). $\int_0^\tau \lambda_0(t) dt < \infty$. 

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C2. (Asymptotic stability). There exist a neighbourhood $\mathcal{B}$ of $\theta_0$, scalar, vector and matrix functions $s^{(0)}$, $s^{(1)}$ and $s^{(2)}$ defined on $\mathcal{B} \times [0, \tau]$ such that for $j = 0, 1, 2$,

$$\sup_{t \in [0, \tau], \theta \in \mathcal{B}} \| S^{(j)}(\theta, t) - s^{(j)}(\theta, t) \| \xrightarrow{P} 0.$$ 

C3. (Lindeberg condition). There exists $\delta > 0$ such that

$$n^{-1/2} \sup_{i, t} |V_i| \ Y_i(t) I \left\{ \theta_0^T V_i > -\delta |V_i| \right\} \xrightarrow{P} 0.$$ 

C4. (Asymptotic regularity conditions). Let $\mathcal{B}$, $s^{(0)}$, $s^{(1)}$ and $s^{(2)}$ be as in condition C2 and define $e = s^{(1)}/s^{(0)}$ and $v = s^{(2)}/s^{(0)} - e \otimes 2$. For all $\theta \in \mathcal{B}$, $t \in [0, \tau]$:

$$s^{(1)}(\theta, t) = \frac{\partial}{\partial \theta} s^{(0)}(\theta, t), \quad s^{(2)}(\theta, t) = \frac{\partial^2}{\partial \theta^2} s^{(0)}(\theta, t),$$

$s^{(0)}(\cdot, t)$, $s^{(1)}(\cdot, t)$ and $s^{(2)}(\cdot, t)$ are continuous functions of $\theta \in \mathcal{B}$, uniformly in $t \in [0, \tau]$, $s^{(0)}$, $s^{(1)}$ and $s^{(2)}$ are bounded on $\mathcal{B} \times [0, \tau]$, $s^{(0)}$ is bounded away from zero on $\mathcal{B} \times [0, \tau]$, and the matrix

$$\Sigma = \int_0^\tau v(\theta_0, t) s^{(0)}(\theta_0, t) \lambda_0(t) \, dt$$

is positive definite.

C5. $p(u)$ and $\phi(u)$ are bounded away from zero and have bounded second derivatives.

C6. $\int_{-\infty}^\infty K(x) \, dx = 1$, $\int_{-\infty}^\infty x K(x) \, dx = 0$ and $\int_{-\infty}^\infty x^2 K(x) \, dx < \infty$.

C7. The kernel function satisfies condition $K_1$ in Giné & Guillou (2002). Let

$$\mathcal{K} = \left\{ y \mapsto K \left( \frac{x - y}{h_n} \right) : x \in R, h_n > 0 \right\},$$

then for any $\epsilon > 0$, $\mathcal{K}$ satisfies that

$$\sup_P N(\mathcal{K}, L_2(P), \epsilon \| F \|_{L_2(P)}) \leq \left( \frac{A}{\epsilon} \right)^\nu$$

for some positive constants $A$ and $\nu$, where $N(\Omega, d, \epsilon)$ denotes the $\epsilon$-covering number of the metric space $(\Omega, d)$, $F$ is the envelope function of $\mathcal{K}$, the supremum is taken over $R$ and the norm $\| F \|_{L_2(P)}^2$ is defined as $\int_P |F(x)|^2 \, dP(x)$.

C8. $| \log h_n | / \log \log n \to \infty$ and $nh_n / | \log h_n | \to \infty$; $h_n$ and $(nh_n)^{-1}$ monotonically converge to zero as $n \to \infty$.

C9. $E(X)$ and $E(Z_i)$ ($i = 1, \ldots, p$) are bounded away from 0.

These conditions are mild and can be satisfied in most of circumstances. Conditions C1-C4 are essential for the asymptotic results of Cox proportional hazards regression model. Condition C5 is a mild smoothness condition on the involved functions. Condition C6 is common for a kernel function and C7 is to regularize
the complexity of the kernel function so that the supremum norm for kernel functions can be bounded in probability, which are also imposed in Chen et al. (2016) and Chen, Genovese, & Wasserman (2018). Specially, the Gauss kernel function satisfies the Conditions C6 and C7. Condition C8 states that the bandwidth $h_n$ converges to zero at certain rate with respect to the sample size $n$. Condition C9 is necessary in the study of covariate-adjusted problems, see Sentürk & Müller (2006).

Appendix B: Proofs of asymptotic properties

As a preparation, we state a lemma, which is extracted from Lemma B.2 of Zhang, Zhu, & Liang (2012) and frequently used in the process of the proof.

**Lemma 1.** Let $\eta(z)$ be a continuous function satisfying $E[|\eta(Z)|^2] < \infty$. Assume that conditions C5–C9 hold. The following asymptotic representation holds:

$$
\frac{1}{n} \sum_{i=1}^{n} (\hat{X}_i - X_i)\eta(Z_i) = \frac{1}{n} \sum_{i=1}^{n} (\tilde{X}_i - X_i) \frac{E[X\eta(Z)]}{E(X)} + o_p(n^{-1/2}).
$$

**Proof of Theorem 1**

**Proof of (i).** Denote by $\theta = (\beta^T, \gamma)^T$, $V = (Z^T, X)^T$ and $\hat{V} = (Z^T, \hat{X})^T$, the log partial likelihood of this covariate-adjusted Cox model can be written as

$$
\hat{L}_n(\beta, \gamma) = \sum_{i=1}^{n} \int_{0}^{\tau} \hat{V}_i^T \theta \ dN_i(t) - \int_{0}^{\tau} \log \left\{ \sum_{i=1}^{n} Y_i(t) \exp(\hat{V}_i^T \theta) \right\} \ d\hat{N}(t).
$$

Set

$$
L_n(\beta, \gamma) = \sum_{i=1}^{n} \int_{0}^{\tau} V_i^T \theta \ dN_i(t) - \int_{0}^{\tau} \log \left\{ \sum_{i=1}^{n} Y_i(t) \exp(V_i^T \theta) \right\} \ dN(t).
$$

The main point of the proof lies in stating that, for any $\theta \in \Theta$,

$$
\hat{L}_n(\beta, \gamma) - L_n(\beta, \gamma) = o_p(n).
$$

This implies, by the fact that $\hat{\theta} = \arg\max_{\theta \in \Theta} \hat{L}_n(\beta, \gamma)$ and the consistency of Cox model under conditions C1–C4, the consistency of $\hat{\theta}$ follows from Lemma 1 of Wu (1981). The detailed proof were given in the supplementary material.

**Proof of (ii).** Let

$$
\hat{U}(\theta) = \sum_{i=1}^{n} \int_{0}^{\tau} \hat{V}_i \ dN_i(t) - \int_{0}^{\tau} \sum_{i=1}^{n} Y_i(t) \hat{V}_i \cdot \frac{\exp(\hat{V}_i^T \theta)}{\sum_{i=1}^{n} Y_i(t) \exp(\hat{V}_i^T \theta)} \ d\hat{N}(t).
$$

By Taylor expansion, there exists $\theta^*$ between $\theta_0$ and $\hat{\theta}$ such that

$$
\frac{1}{\sqrt{n}} \hat{U}(\hat{\theta}) - \frac{1}{\sqrt{n}} \hat{U}(\theta_0) = \frac{1}{n} \frac{\partial \hat{U}(\theta^*)}{\partial \theta} \sqrt{n}(\hat{\theta} - \theta_0).
$$
By the definition of \( \hat{\theta} \), we know that \( \hat{U}(\hat{\theta}) = 0 \). So we have

\[
\sqrt{n}(\hat{\theta} - \theta_0) = \left\{ \frac{1}{n} \frac{\partial \hat{U}(\theta^*)}{\partial \theta} \right\}^{-1} \cdot \frac{1}{\sqrt{n}} \hat{U}(\theta_0).
\]

We can prove that

\[
-\frac{1}{n} \frac{\partial \hat{U}(\theta^*)}{\partial \theta} \xrightarrow{p} \Sigma, \tag{8}
\]

and

\[
\frac{1}{\sqrt{n}} \hat{U}(\theta_0) \xrightarrow{d} N(0, \Sigma + \Omega), \tag{9}
\]

where \( \Sigma = \begin{pmatrix} \Sigma_{11} & \Sigma_{12} \\ \Sigma_{21} & \Sigma_{22} \end{pmatrix} \) is defined in condition C4, \( \zeta = (-\Sigma_{22}^T\gamma_0, -\Sigma_{12}^T\gamma_0)^T \) and \( \Omega = \frac{\text{Var}(X) - \text{Var}(\tilde{X})}{\{E(X)\}^2} \zeta \zeta^T \).

Combining (8) and (9), we have

\[
\sqrt{n}(\hat{\theta} - \theta_0) \xrightarrow{d} N(0, \Sigma^{-1}(\Sigma + \Omega)\Sigma^{-1}),
\]

where

\[
\Sigma^{-1}(\Sigma + \Omega)\Sigma^{-1} = \Sigma^{-1}\Sigma\Sigma^{-1} + \frac{\text{Var}(\tilde{X}) - \text{Var}(X)}{\{E(X)\}^2} \Sigma^{-1} \zeta \zeta^T \Sigma^{-1}
\]

\[
= \Sigma^{-1}\Sigma\Sigma^{-1} + \frac{\text{Var}(\tilde{X}) - \text{Var}(X)}{\{E(X)\}^2} \begin{pmatrix} 0 & \cdots & 0 & 0 \\ \vdots & & \vdots & 0 \\ 0 & \cdots & 0 & 0 \\ 0 & \cdots & 0 & \gamma_0^2 \end{pmatrix}.
\]

We can obtain that

\[
\sqrt{n}(\hat{\beta} - \beta_0) \xrightarrow{d} N(0, (\Sigma^{-1}_p)_p),
\]

and

\[
\sqrt{n}(\hat{\gamma} - \gamma_0) \xrightarrow{d} N\left(0, (\Sigma^{-1}(\Sigma^{-1})_{(p+1,p+1)} + \frac{\text{Var}(\tilde{X}) - \text{Var}(X)}{\{E(X)\}^2} \gamma_0^2 \right),
\]

where \((\Sigma^{-1})_p\) and \((\Sigma^{-1})_{(p+1,p+1)}\) respectively represent the \(p\)th order sequential principal minor and the \((p + 1)\)th diagonal element of matrix \(\Sigma^{-1}\). The detailed proof of (8) and (9) were given in the supplementary material.

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Figure 1: Kaplan-Meier survival curves stratified by two different histological types of the tumor in the NWTS

The graph shows two survival curves, one for unfavorable conditions and another for favorable conditions, plotted against time to death in years. The survival probability is indicated on the y-axis, ranging from 0.0 to 1.0, and time to death is on the x-axis, ranging from 0 to 20 years.
Figure 2: The scatter diagram of tumor bearing specimen’s weight (wgt) versus tumor’s diameter (diam) for the NWTSG trials.
Table 1: Simulation results for $\beta$ and $\gamma$ under sample size $n = 100$

| CR     | Method | Para. | $\phi(u) = (u + 3)/7$ | $\phi(u) = 3(u + 1)^2/79$ |
|--------|--------|-------|------------------------|--------------------------|
|        |        |       | Bias | SD | SE | MSE | CP |       | Bias | SD | SE | MSE | CP |
| 20%    | Proposed | $\beta_1$ | 0.020 | 0.224 | 0.222 | 0.051 | 0.960 | 0.006 | 0.225 | 0.221 | 0.051 | 0.946 |
|        |         | $\beta_2$ | 0.007 | 0.211 | 0.206 | 0.044 | 0.942 | 0.001 | 0.212 | 0.206 | 0.045 | 0.943 |
|        |         | $\gamma$ | 0.021 | 0.286 | 0.278 | 0.082 | 0.946 | -0.047 | 0.292 | 0.267 | 0.087 | 0.906 |
|        | Naive   | $\beta_1$ | -0.006 | 0.224 | 0.221 | 0.050 | 0.945 | -0.089 | 0.223 | 0.217 | 0.058 | 0.911 |
|        |         | $\beta_2$ | -0.007 | 0.211 | 0.206 | 0.044 | 0.948 | -0.045 | 0.211 | 0.205 | 0.047 | 0.933 |
|        |         | $\gamma$ | -0.217 | 0.254 | 0.235 | 0.112 | 0.780 | -0.810 | 0.171 | 0.160 | 0.686 | 0.006 |
|        | Oracle  | $\beta_1$ | 0.030 | 0.222 | 0.222 | 0.050 | 0.953 | 0.030 | 0.222 | 0.222 | 0.050 | 0.953 |
|        |         | $\beta_2$ | 0.011 | 0.210 | 0.206 | 0.044 | 0.936 | 0.011 | 0.210 | 0.206 | 0.044 | 0.936 |
|        |         | $\gamma$ | 0.044 | 0.276 | 0.279 | 0.078 | 0.952 | 0.044 | 0.276 | 0.279 | 0.078 | 0.952 |
| 40%    | Proposed | $\beta_1$ | 0.024 | 0.259 | 0.253 | 0.068 | 0.944 | 0.011 | 0.260 | 0.252 | 0.068 | 0.941 |
|        |         | $\beta_2$ | 0.012 | 0.251 | 0.237 | 0.063 | 0.932 | 0.007 | 0.251 | 0.237 | 0.063 | 0.939 |
|        |         | $\gamma$ | 0.031 | 0.334 | 0.316 | 0.113 | 0.937 | -0.042 | 0.341 | 0.303 | 0.118 | 0.897 |
|        | Naive   | $\beta_1$ | 0.001 | 0.258 | 0.251 | 0.067 | 0.946 | -0.073 | 0.256 | 0.247 | 0.071 | 0.920 |
|        |         | $\beta_2$ | 0.000 | 0.250 | 0.237 | 0.063 | 0.942 | -0.034 | 0.250 | 0.236 | 0.063 | 0.933 |
|        |         | $\gamma$ | -0.220 | 0.299 | 0.265 | 0.137 | 0.791 | -0.824 | 0.200 | 0.180 | 0.718 | 0.026 |
|        | Oracle  | $\beta_1$ | 0.034 | 0.257 | 0.253 | 0.067 | 0.942 | 0.034 | 0.257 | 0.253 | 0.067 | 0.942 |
|        |         | $\beta_2$ | 0.015 | 0.250 | 0.237 | 0.063 | 0.928 | 0.015 | 0.250 | 0.237 | 0.063 | 0.928 |
|        |         | $\gamma$ | 0.050 | 0.324 | 0.315 | 0.107 | 0.951 | 0.050 | 0.324 | 0.315 | 0.107 | 0.951 |
| 80%    | Proposed | $\beta_1$ | 0.072 | 0.454 | 0.436 | 0.212 | 0.932 | 0.065 | 0.461 | 0.435 | 0.217 | 0.931 |
|        |         | $\beta_2$ | 0.031 | 0.454 | 0.413 | 0.207 | 0.914 | 0.028 | 0.452 | 0.412 | 0.205 | 0.912 |
|        |         | $\gamma$ | 0.107 | 0.589 | 0.542 | 0.359 | 0.939 | 0.020 | 0.572 | 0.517 | 0.328 | 0.927 |
|        | Naive   | $\beta_1$ | 0.059 | 0.466 | 0.434 | 0.221 | 0.930 | 0.012 | 0.460 | 0.428 | 0.212 | 0.927 |
|        |         | $\beta_2$ | 0.022 | 0.450 | 0.413 | 0.203 | 0.913 | 0.002 | 0.449 | 0.410 | 0.201 | 0.915 |
|        |         | $\gamma$ | -0.183 | 0.507 | 0.449 | 0.291 | 0.883 | -0.830 | 0.340 | 0.304 | 0.805 | 0.254 |
|        | Oracle  | $\beta_1$ | 0.080 | 0.460 | 0.437 | 0.218 | 0.935 | 0.080 | 0.460 | 0.437 | 0.218 | 0.935 |
|        |         | $\beta_2$ | 0.033 | 0.458 | 0.414 | 0.211 | 0.909 | 0.033 | 0.458 | 0.414 | 0.211 | 0.909 |
|        |         | $\gamma$ | 0.125 | 0.592 | 0.539 | 0.366 | 0.939 | 0.125 | 0.592 | 0.539 | 0.366 | 0.939 |

The true value of the parameters $\beta_1 = 1$, $\beta_2 = 0.5$, $\gamma = 1.5$; $\phi(\cdot)$, the distortion function; CR, the censoring rate; Bias, the estimate value minus the true value; SD, the standard deviation; SE, the estimate of SD; MSE, the mean-square error; CP, empirical coverage percentage of the 95% confidence interval.
Table 2: Simulation results for $\beta$ and $\gamma$ under sample size $n = 200$

| CR  | Method | Para. | $\phi(u) = (u + 3)/7$ | $\phi(u) = 3(u + 1)^2/79$ |
|-----|--------|-------|------------------------|------------------------|
|     |        |       | Bias       | SD      | SE     | MSE     | CP       | Bias       | SD      | SE     | MSE     | CP       |
| 20% | Proposed | $\beta_1$ | 0.009 0.156 0.151 0.024 0.939 | 0.004 0.157 0.151 0.025 0.936 |
|     |        | $\beta_2$ | 0.004 0.151 0.142 0.023 0.936 | 0.002 0.152 0.142 0.023 0.935 |
|     |        | $\gamma$ | 0.006 0.196 0.190 0.039 0.949 | -0.021 0.202 0.186 0.041 0.932 |
|     | Naive | $\beta_1$ | -0.017 0.158 0.150 0.025 0.932 | -0.094 0.158 0.147 0.034 0.865 |
|     |        | $\beta_2$ | -0.009 0.152 0.141 0.023 0.930 | -0.049 0.153 0.140 0.026 0.907 |
|     |        | $\gamma$ | -0.234 0.178 0.159 0.087 0.649 | -0.812 0.122 0.108 0.674 0.000 |
|     | Oracle | $\beta_1$ | 0.015 0.154 0.151 0.024 0.935 | 0.015 0.154 0.151 0.024 0.935 |
|     |        | $\beta_2$ | 0.007 0.150 0.142 0.022 0.939 | 0.007 0.150 0.142 0.022 0.939 |
|     |        | $\gamma$ | 0.021 0.190 0.190 0.036 0.948 | 0.021 0.190 0.190 0.036 0.948 |
| 40% | Proposed | $\beta_1$ | 0.015 0.177 0.172 0.032 0.941 | 0.010 0.178 0.172 0.032 0.938 |
|     |        | $\beta_2$ | 0.002 0.169 0.163 0.029 0.946 | -0.001 0.170 0.163 0.029 0.945 |
|     |        | $\gamma$ | 0.015 0.225 0.215 0.051 0.944 | -0.013 0.228 0.211 0.052 0.928 |
|     | Naive | $\beta_1$ | -0.007 0.180 0.171 0.032 0.929 | -0.074 0.181 0.168 0.038 0.892 |
|     |        | $\beta_2$ | -0.010 0.171 0.162 0.029 0.936 | -0.046 0.172 0.161 0.032 0.921 |
|     |        | $\gamma$ | -0.235 0.199 0.179 0.095 0.698 | -0.822 0.134 0.122 0.693 0.001 |
|     | Oracle | $\beta_1$ | 0.021 0.175 0.172 0.031 0.940 | 0.021 0.175 0.172 0.031 0.940 |
|     |        | $\beta_2$ | 0.005 0.168 0.163 0.028 0.945 | 0.005 0.168 0.163 0.028 0.945 |
|     |        | $\gamma$ | 0.028 0.220 0.215 0.049 0.948 | 0.028 0.220 0.215 0.049 0.948 |
| 80% | Proposed | $\beta_1$ | 0.022 0.294 0.293 0.087 0.957 | 0.020 0.294 0.293 0.087 0.958 |
|     |        | $\beta_2$ | 0.014 0.285 0.283 0.081 0.952 | 0.012 0.285 0.282 0.082 0.948 |
|     |        | $\gamma$ | 0.023 0.383 0.360 0.147 0.934 | -0.010 0.383 0.353 0.147 0.914 |
|     | Naive | $\beta_1$ | 0.011 0.294 0.292 0.087 0.951 | -0.028 0.293 0.289 0.087 0.943 |
|     |        | $\beta_2$ | 0.006 0.285 0.282 0.081 0.943 | -0.018 0.285 0.280 0.082 0.941 |
|     |        | $\gamma$ | -0.247 0.327 0.298 0.168 0.816 | -0.850 0.223 0.202 0.773 0.035 |
|     | Oracle | $\beta_1$ | 0.026 0.293 0.293 0.086 0.955 | 0.026 0.293 0.293 0.086 0.955 |
|     |        | $\beta_2$ | 0.017 0.284 0.282 0.081 0.951 | 0.017 0.284 0.282 0.081 0.951 |
|     |        | $\gamma$ | 0.036 0.376 0.360 0.143 0.941 | 0.036 0.376 0.360 0.143 0.941 |

The true value of the parameters $\beta_1 = 1$, $\beta_2 = 0.5$, $\gamma = 1.5$; $\phi(\cdot)$, the distortion function; CR, the censoring rate; Bias, the estimate value minus the true value; SD, the standard deviation; SE, the estimate of SD; MSE, the mean-square error; CP, empirical coverage percentage of the 95% confidence interval.
Table 3: The data of the NWTSG trials grouped by the histological type

|                   | overall | favorable | unfavorable |
|-------------------|---------|-----------|-------------|
| size              | 3915    | 3476      | 439         |
| wgt               | 604.56  | 603.74    | 611.12      |
| diam              | 11.21   | 11.20     | 11.32       |
| age               | 3.53    | 3.52      | 3.68        |
| stage(%)          | 64.78   | 66.28     | 52.85       |
| num(%)            | 42.68   | 42.55     | 43.74       |
| time              | 10.33   | 10.68     | 7.55        |
| cen.rate (%)      | 88.66   | 92.23     | 60.36       |

overall, the total patients; favorable, the patients with favorable tumor; unfavorable, the patients with unfavorable tumor; size, the sample size; wgt, the mean weight of tumor bearing specimens; diam, the mean diameter of tumors; age, the mean age of patients at diagnosis; stage, the percentage of patients with tumor localized spread; num, the percentage of patients in NWTS-3 trial; time, the mean observed time; cen.rate, the censoring rate.

Table 4: The analysis results of the covariate effects in the NWTSG trials

| Method | Covariate | EST   | SE   | P-value |
|--------|-----------|-------|------|---------|
| Proposed | wgt       | -0.482| 0.180| 0.008   |
|         | type      | 1.820 | 0.096| < 0.001 |
|         | stage     | -0.900| 0.097| < 0.001 |
|         | age       | 0.070 | 0.020| < 0.001 |
|         | num       | 0.171 | 0.098| 0.081   |
| Naive   | wgt       | -0.139| 0.119| 0.244   |
|         | type      | 1.821 | 0.096| < 0.001 |
|         | stage     | -0.908| 0.099| < 0.001 |
|         | age       | 0.066 | 0.020| 0.001   |
|         | num       | 0.187 | 0.097| 0.055   |

wgt, the weight of tumor bearing specimen; type, the histological type of the tumor; stage, the tumor stage; age, the age of patients at diagnosis; num, the study number; EST, the estimate of the parameters; SE, the standard error estimate; P-value, the p-value of the parameters.
Supplementary material for “Cox regression analysis for distorted covariates with an unknown distortion function”

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This supplementary material contains the detailed proof of Theorem 1.

Proof of Theorem 1

As a preparation, we state a lemma, which is extracted from Lemma B.2 of Zhang, Zhu, & Liang (2012) and frequently used in the process of the proof.

Lemma 1. Let $\eta(z)$ be a continuous function satisfying $E[\eta(Z)^2] < \infty$. Assume that conditions C5–C9 hold. The following asymptotic representation holds:

$$\frac{1}{n} \sum_{i=1}^{n} (\hat{X}_i - X_i) \eta(Z_i) = \frac{1}{n} \sum_{i=1}^{n} (\tilde{X}_i - X_i) \frac{E[X \eta(Z)]}{E(X)} + o_p(n^{-1/2}).$$

Proof of (i). Denote by $\theta = (\beta^T, \gamma)^T$, $V = (Z^T, X)^T$ and $\hat{V} = (Z^T, \hat{X})^T$, the log partial likelihood of this covariate-adjusted Cox model can be written as

$$\hat{L}_n(\beta, \gamma) = \sum_{i=1}^{n} \int_0^\tau \hat{V}_i^T \theta \, dN_i(t) - \int_0^\tau \log \left\{ \sum_{i=1}^{n} Y_i(t) \exp(\hat{V}_i^T \theta) \right\} \, d\hat{N}(t).$$

Set

$$L_n(\beta, \gamma) = \sum_{i=1}^{n} \int_0^\tau V_i^T \theta \, dN_i(t) - \int_0^\tau \log \left\{ \sum_{i=1}^{n} Y_i(t) \exp(V_i^T \theta) \right\} \, dN(t),$$

The main point of the proof lies in stating that, for any $\theta \in \Theta$,

$$\hat{L}_n(\beta, \gamma) - L_n(\beta, \gamma) = o_p(n).$$

This implies, by the fact that $\hat{\theta} = \arg\max_{\theta \in \Theta} \hat{L}_n(\beta, \gamma)$ and the consistency of Cox model under conditions C1–C4, the consistency of $\hat{\theta}$ follows from Lemma 1 of Wu (1981). Now, after simple calculations, we can

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obtain the decomposition
\[
\hat{L}_n(\beta, \gamma) - L_n(\beta, \gamma) = \sum_{i=1}^{n} \int_0^\tau (\gamma \hat{X}_i - \gamma X_i) \, dN_i(t) + \int_0^\tau \log \left\{ \frac{\sum_{i=1}^{n} Y_i(t) \exp(V_i^T \theta)}{\sum_{i=1}^{n} Y_i(t) \exp(\hat{V}_i^T \theta)} \right\} \, d\bar{N}(t) \\
\triangleq F_1 + F_2, \tag{1}
\]
where
\[
F_1 = \sum_{i=1}^{n} \int_0^\tau (\gamma \hat{X}_i - \gamma X_i) \, dN_i(t),
\]
and
\[
F_2 = \int_0^\tau \log \left\{ \frac{\sum_{i=1}^{n} Y_i(t) \exp(V_i^T \theta)}{\sum_{i=1}^{n} Y_i(t) \exp(\hat{V}_i^T \theta)} \right\} \, d\bar{N}(t).
\]
Define
\[
g_X(U) = E(\hat{X}|U)p(U),
\]
then
\[
\hat{g}_X(U) = \frac{1}{nh_n} \sum_{i=1}^{n} K \left( \frac{u - U_i}{h_n} \right) \hat{X}_i.
\]
It follows from Theorem 2 in Chen, Genovese, & Wasserman (2014) that
\[
\sup_u |\hat{g}_X(u) - g_X(u)| = O_P \left( h_n^2 + \frac{\log n}{nh_n} \right). \tag{2}
\]
By Theorem 2.3 in Giné & Guillou (2002), we have
\[
\sup_u |\hat{p}(u) - E\{\hat{p}(u)\}| = O \left( \frac{\log n}{\sqrt{nh_n}} \right), \quad a.s..
\]
On the other hand, under assumption C6, it is well known that
\[
\sup_u |E\{\hat{p}(u)\} - p(u)| = O(h_n^2).
\]
As a consequence, we have
\[
\sup_u |\hat{p}(u) - p(u)| = O \left( h_n^2 + \frac{\log n}{nh_n} \right), \quad a.s.. \tag{3}
\]
Coupled with (2) and (3), some straightforward calculations entail

\[ |F_1| = \left| \sum_{i=1}^{n} \int_{0}^{\tau} \gamma(\hat{X}_i - X_i) \, dN_i(t) \right| = O_p \left\{ \left( h_n^2 + (nh_n)^{-1/2} (\log n)^{1/2} \right) \cdot n \right\} = o_p(n). \] 

(4)

Similarly,

\[ |F_2| = \left| \int_{0}^{\tau} \log \left\{ \frac{1}{n} \sum_{i=1}^{n} Y_i(t) \exp(\beta^T \tilde{Z}_i) \exp(\gamma X_i) \right\} \, d\tilde{N}(t) \right| = O_p \left\{ \left( h_n^2 + (nh_n)^{-1/2} (\log n)^{1/2} \right) \cdot n \right\} = o_p(n). \] 

(5)

Combining (1), (4) and (5), we have

\[ \hat{L}_n(\beta, \gamma) - L_n(\beta, \gamma) = o_p(n). \]

Here, we complete the proof of (i).

Proof of (ii). Let

\[ \hat{U}(\theta) = \sum_{i=1}^{n} \int_{0}^{\tau} \hat{V}_i \, dN_i(t) - \int_{0}^{\tau} \sum_{i=1}^{n} Y_i(t) \hat{V}_i \cdot \exp(\hat{V}_i^T \theta) \sum_{i=1}^{n} Y_i(t) \exp(\hat{V}_i^T \theta) \, d\tilde{N}(t). \]

By Taylor expansion, there exists \( \theta^* \) between \( \theta_0 \) and \( \hat{\theta} \) such that

\[ \frac{1}{\sqrt{n}} \hat{U}(\theta) - \frac{1}{\sqrt{n}} \hat{U}(\theta_0) = \frac{1}{n} \frac{\partial \hat{U}(\theta^*)}{\partial \theta} \sqrt{n}(\hat{\theta} - \theta_0). \]

By the definition of \( \hat{\theta} \), we know that \( \hat{U}(\theta) = 0 \). So we have

\[ \sqrt{n}(\hat{\theta} - \theta_0) = \left\{ -\frac{1}{n} \frac{\partial \hat{U}(\theta^*)}{\partial \theta} \right\}^{-1} \cdot \frac{1}{\sqrt{n}} \hat{U}(\theta_0). \]

In order to prove the asymptotic normality, it suffices to show that

\[ \left\{ -\frac{1}{n} \frac{\partial \hat{U}(\theta^*)}{\partial \theta} \right\}^{-1} \xrightarrow{p} \text{a non-singular matrix}, \]

and

\[ \frac{1}{\sqrt{n}} \hat{U}(\theta_0) \xrightarrow{d} \text{a Gaussian distribution}. \]
We introduce some notations:

\[
\begin{align*}
\hat{S}^{(0)}(\theta, t) &= \frac{1}{n} \sum_{i=1}^{n} Y_i(t) \exp \left( \tilde{V}_i^T \theta \right), \\
S^{(l)}_X(\theta, t) &= \frac{1}{n} \sum_{i=1}^{n} Y_i(t) X_i^{\otimes l} \exp \left( V_i^T \theta \right), \\
\hat{S}^{(l)}_X(\theta, t) &= \frac{1}{n} \sum_{i=1}^{n} Y_i(t) \tilde{X}_i^{\otimes l} \exp \left( \tilde{V}_i^T \theta \right), \\
S^{(l)}_Z(\theta, t) &= \frac{1}{n} \sum_{i=1}^{n} Y_i(t) Z_i^{\otimes l} \exp \left( V_i^T \theta \right), \\
\hat{S}^{(l)}_Z(\theta, t) &= \frac{1}{n} \sum_{i=1}^{n} Y_i(t) Z_i^{\otimes l} \exp \left( \tilde{V}_i^T \theta \right), \\
S^{(l_1,l_2)}_Z(\theta, t) &= \frac{1}{n} \sum_{i=1}^{n} Y_i(t) Z_i^{\otimes l_1} X_i^{\otimes l_2} \exp \left( V_i^T \theta \right), \\
\hat{S}^{(l_1,l_2)}_Z(\theta, t) &= \frac{1}{n} \sum_{i=1}^{n} Y_i(t) Z_i^{\otimes l_1} \tilde{X}_i^{\otimes l_2} \exp \left( \tilde{V}_i^T \theta \right),
\end{align*}
\]

\(s^{(l)}_X(\theta, t), s^{(l)}_Z(\theta, t)\) and \(s^{(l_1,l_2)}_Z(\theta, t)\) are defined the same as \(s^{(0)}, s^{(1)}\) and \(s^{(2)}\) in condition C2, where \(l, l_1, l_2 = 1, 2, 3\).

Straightforward calculations entail

\[
\begin{align*}
&\left\| \hat{S}^{(0)}(\theta, t) - S^{(0)}(\theta, t) \right\| \\
= &\left\| \frac{1}{n} \sum_{i=1}^{n} Y_i(t) \exp(\beta^T Z_i) \left\{ \exp(\gamma \tilde{X}_i) - \exp(\gamma X_i) \right\} \right\| \\
= &\left\| \frac{1}{n} \sum_{i=1}^{n} Y_i(t) \exp(\beta^T Z_i) \left\{ \gamma \exp(\gamma X_i) (\tilde{X}_i - X_i) + \frac{1}{2} \gamma^2 \exp(\gamma X_i^*) (\tilde{X}_i - X_i)^2 \right\} \right\| \\
\leq &\left\| \frac{1}{n} \sum_{i=1}^{n} Y_i(t) \exp(\tilde{V}_i^T \theta) \cdot \gamma \cdot (\tilde{X}_i - X_i) \right\| + o_p \left( n^{-1/2} \right) \\
\leq &\left\| \frac{1}{n} \sum_{i=1}^{n} (\tilde{X}_i - X_i) \frac{E \left\{ X_i \exp(V_i^T \theta) \gamma \right\}}{E(X)} \right\| + o_p \left( n^{-1/2} \right) + o_p \left( n^{-1/2} \right) \\
= &\left\| \sum_{i=1}^{n} (\tilde{X}_i - X_i) \frac{s^{(1)}_X(\theta, t) \cdot \gamma}{n E(X)} \right\| + o_p \left( n^{-1/2} \right),
\end{align*}
\]

where \(X_i^* = \tilde{X}_i + t_i^*(\tilde{X}_i - X_i)\) for some \(t_i^* \in (0, 1)\). Set \(Q_n = \frac{\sum_{i=1}^{n} (\tilde{X}_i - X_i)}{E(X)}\), then

\[
\sup_{\theta \in \Theta, t \in [0, T]} \left| \hat{S}^{(0)}(\theta, t) - S^{(0)}(\theta, t) \right| \leq \sup_{\theta \in \Theta, t \in [0, T]} \left| \frac{s^{(1)}_X(\theta, t) \cdot \gamma}{n} Q_n \right| + o_p \left( n^{-1/2} \right) = o_p (1).
\]
Likewise, it holds uniformly over \((\theta, t) \in \mathcal{B} \times [0, \tau]\) that

\[
\begin{align*}
&\left\| \hat{S}^{(1)}_Z(\theta, t) - S^{(1)}_Z(\theta, t) \right\| \leq \left\| \frac{s^{(1)}_{Z, \theta}(\theta, t)}{n} \cdot \gamma Q_n \right\| + o_p \left( n^{-1/2} \right) = o_p(1), \\
&\left\| \hat{S}^{(1)}_X(\theta, t) - S^{(1)}_X(\theta, t) \right\| \leq \left\| \frac{s^{(1)}_{X, \theta}(\theta, t)}{n} Q_n \right\| + \left\| \frac{\gamma \cdot s^{(2)}_{Z, \theta}(\theta, t)}{n} Q_n \right\| + o_p \left( n^{-1/2} \right) = o_p(1), \\
&\left\| \hat{S}^{(2)}_Z(\theta, t) - S^{(2)}_Z(\theta, t) \right\| \leq \left\| \frac{\gamma \cdot s^{(2)}_{Z, \theta}(\theta, t)}{n} Q_n \right\| + o_p \left( n^{-1/2} \right) = o_p(1), \\
&\left\| \hat{S}^{(2)}_X(\theta, t) - S^{(2)}_X(\theta, t) \right\| \leq \left\| \frac{2s^{(2)}_{X, \theta}(\theta, t)}{n} Q_n \right\| + \left\| \frac{\gamma s^{(3)}_{X, \theta}(\theta, t)}{n} Q_n \right\| + o_p \left( n^{-1/2} \right) = o_p(1), \\
&\left\| \hat{S}^{(1)}_{Z, X}(\theta, t) - S^{(1)}_{Z, X}(\theta, t) \right\| \leq \left\| \frac{s^{(1, 1)}_{Z, X}(\theta, t)}{n} Q_n \right\| + \left\| \frac{\gamma s^{(1, 2)}_{Z, X}(\theta, t)}{n} Q_n \right\| + o_p \left( n^{-1/2} \right) = o_p(1).
\end{align*}
\]

For simplicity, we define

\[
\hat{G}(\theta, t) = \left( \begin{array}{c}
\hat{S}^{(2)}_{Z, \theta}(\theta, t) - \frac{s^{(1)}_{Z, \theta}(\theta, t)}{n} \left\{ \frac{s^{(1)}_{Z, \theta}(\theta, t)}{n} T \right. \\
S^{(0)}(\theta, t)
\end{array} \right) \left( \begin{array}{c}
\hat{S}^{(1)}_{X, \theta}(\theta, t) - \frac{s^{(1)}_{Z, \theta}(\theta, t)}{n} \left\{ \frac{s^{(1)}_{Z, \theta}(\theta, t)}{n} T \right. \\
S^{(0)}(\theta, t)
\end{array} \right)^T,
\]

and

\[
G(\theta, t) = \left( \begin{array}{c}
\hat{S}^{(2)}_{Z, \theta}(\theta, t) - \frac{s^{(1)}_{Z, \theta}(\theta, t)}{n} \left\{ \frac{s^{(1)}_{Z, \theta}(\theta, t)}{n} T \right. \\
S^{(0)}(\theta, t)
\end{array} \right) \left( \begin{array}{c}
\hat{S}^{(1)}_{X, \theta}(\theta, t) - \frac{s^{(1)}_{Z, \theta}(\theta, t)}{n} \left\{ \frac{s^{(1)}_{Z, \theta}(\theta, t)}{n} T \right. \\
S^{(0)}(\theta, t)
\end{array} \right)^T.
\]

Therefore, we obtain that \( \sup_{\theta \in \mathcal{B}, t \in [0, \tau]} \left\| \hat{G}(\theta, t) - G(\theta, t) \right\| = o_p(1) \). Noting that

\[
\frac{\partial \hat{U}(\theta)}{\partial \theta} = -\int_0^\tau \hat{G}(\theta, t) d\hat{N}(t),
\]

we have

\[
\sup_{\theta \in \mathcal{B}, t \in [0, \tau]} \left\| \frac{\partial \hat{U}(\theta)}{\partial \theta} - \frac{\partial U(\theta)}{\partial \theta} \right\| = o_p(n).
\]

It readily to show that

\[
-\frac{1}{n} \frac{\partial \hat{U}(\theta^*)}{\partial \theta} \xrightarrow{p} \Sigma,
\]

where \( \Sigma = \begin{pmatrix} \Sigma_{11} & \Sigma_{12} \\ \Sigma_{21} & \Sigma_{22} \end{pmatrix} \) is defined in condition C4.
For the second part of the proof, note that
\[
\hat{U}(\theta_0) = \sum_{i=1}^{n} \int_{0}^{\tau} \tilde{V}_i \, dN_i(t) - \int_{0}^{\tau} \frac{\sum_{i=1}^{n} Y_i(t) \tilde{V}_i \cdot \exp(\tilde{V}_i^T \theta_0)}{\sum_{i=1}^{n} Y_i(t) \exp(\tilde{V}_i^T \theta_0)} \, d\tilde{N}(t),
\]
and
\[
U(\theta_0) = \sum_{i=1}^{n} \int_{0}^{\tau} V_i \, dN_i(t) - \int_{0}^{\tau} \frac{\sum_{i=1}^{n} Y_i(t) V_i \cdot \exp(V_i^T \theta_0)}{\sum_{i=1}^{n} Y_i(t) \exp(V_i^T \theta_0)} \, d\tilde{N}(t).
\]
Straightforward calculations entail
\[
\hat{U}(\theta_0) - U(\theta_0) = \begin{pmatrix}
\frac{1}{\sum_{i=1}^{n} \int_{0}^{\tau} \left\{ S_Z^{(1)}(\theta_0, t)/S^{(0)}(\theta_0, t) - \tilde{S}_Z^{(1)}(\theta_0, t)/\tilde{S}^{(0)}(\theta_0, t) \right\} d\tilde{N}(t)
\end{pmatrix}
\end{pmatrix} \triangleq \begin{pmatrix}
D_1 \\
D_2
\end{pmatrix},
\]
where
\[
D_1 = \int_{0}^{\tau} \left\{ S_Z^{(1)}(\theta_0, t)/S^{(0)}(\theta_0, t) - \tilde{S}_Z^{(1)}(\theta_0, t)/\tilde{S}^{(0)}(\theta_0, t) \right\} d\tilde{N}(t),
\]
and
\[
D_2 = \sum_{i=1}^{n} \int_{0}^{\tau} \left\{ (\tilde{X}_i - X_i) + S_X^{(1)}(\theta_0, t)/S^{(0)}(\theta_0, t) - \tilde{S}_X^{(1)}(\theta_0, t)/\tilde{S}^{(0)}(\theta_0, t) \right\} dN_i(t).
\]
Using the first order expansion yields
\[
\frac{x}{y} = \frac{x_0}{y_0} + \frac{x - x_0}{y_0} - \frac{(y - y_0)x_0}{y_0^2} + o \left\{ \sqrt{(x - x_0)^2 - (y - y_0)^2} \right\}.
\]
Then
\[
\\
= \frac{\tilde{S}_Z^{(1)}(\theta_0, t) - S_Z^{(1)}(\theta_0, t)}{S^{(0)}(\theta_0, t)} \triangleq \begin{pmatrix}
\frac{\tilde{S}_Z^{(1)}(\theta_0, t) - S_Z^{(1)}(\theta_0, t)}{S^{(0)}(\theta_0, t)} - \left\{ \frac{S^{(0)}(\theta_0, t) - S^{(0)}(\theta_0, t)}{S^{(0)}(\theta_0, t)} \right\} \frac{s_Z^{(1)}(\theta_0, t)}{S^{(0)}(\theta_0, t)} + o_p(1)
\end{pmatrix}
\end{pmatrix} \triangleq \begin{pmatrix}
D_1 \\
D_2
\end{pmatrix},
\]
and
\[
\gamma_0 Q_n \frac{1}{n} \left[ \left\{ \frac{s_X^{(1)}(\theta_0, t)}{S^{(0)}(\theta_0, t)} - \frac{s_X^{(1)}(\theta_0, t) S_Z^{(1)}(\theta_0, t)}{S^{(0)}(\theta_0, t)} \right\} + o_p(1) \right] \triangleq \begin{pmatrix}
D_1 \\
D_2
\end{pmatrix},
\]
holds uniformly over \( t \in [0, \tau] \). For simplicity, we define
\[
G_{12} = \frac{S_{Z^1X}^{(1,1)}(\theta_0,t)}{S^{(0)}(\theta_0,t)} - \frac{S_X^{(1)}(\theta_0,t)S_Z^{(1)}(\theta_0,t)}{\{S^{(0)}(\theta_0,t)\}^2},
\]
then
\[
D_1 = \int_0^\tau - \frac{\gamma_0Q_n}{n}G_{12}d\tilde{N}(t) + o_p(1)
= -\gamma_0Q_n\Sigma_{12} + o_p(1).
\]
Similarly
\[
D_2 = \sum_{i=1}^n \int_0^\tau \left\{ (\tilde{X}_i - X_i) + \frac{S_{Z^1X}^{(1)}(\theta_0,t)}{S^{(0)}(\theta_0,t)} - \frac{S_X^{(1)}(\theta_0,t)}{S^{(0)}(\theta_0,t)} \right\} dN_i(t)
= E\{XN(\tau)\}Q_n - \sum_{i=1}^n \int_0^\tau \frac{S_X^{(1)}(\theta_0,t)}{S^{(0)}(\theta_0,t)} \cdot \frac{Q_n}{n} dN_i(t) - \gamma_0Q_n\Sigma_{22} + o_p(1)
= E \left\{ \int_0^\tau \left( X - \frac{S_X^{(1)}(\theta_0,t)}{S^{(0)}(\theta_0,t)} \right) dN(t) \right\} Q_n - \gamma_0Q_n\Sigma_{22} + o_p(1)
= -\gamma_0Q_n\Sigma_{22} + o_p(1).
\]
Hence,
\[
n^{-1/2} \left\{ \hat{U}(\theta_0) - U(\theta_0) \right\} = n^{-1/2}Q_n \begin{pmatrix} -\Sigma_{12}\gamma_0 \\ -\Sigma_{22}\gamma_0 \end{pmatrix} + o_p(1).
\]
Let \( \zeta = (-\Sigma_{12}\gamma_0, -\Sigma_{22}\gamma_0)^T \), then
\[
n^{-1/2}\hat{U}(\theta_0) = n^{-1/2}\sum_{i=1}^n \int_0^\tau \left\{ V_i - \frac{S_X^{(1)}(\theta_0,t)}{S^{(0)}(\theta_0,t)} \right\} dN_i(t) + n^{-1/2}Q_n\zeta + o_p(1).
\]
Set
\[
\mathcal{F}_t = \sigma \{ N_i(t), N_i^C(t), Z_i, X_i; 0 \leq t \leq \tau, i = 1, \ldots, n \}.
\]
The processes \( M_i(t) \) defined by
\[
M_i(t) = N_i(t) - \int_0^t \lambda_i(u)du, \; i = 1, \ldots, n, \; t \in [0, \tau]
\]
are local martingales on the time interval \([0, \tau]\). As a consequence, they are in fact local square integrable martingales. Furthermore, because of \( U \) is independent with \( (\tilde{T}, C, Z, X) \), we define
\[
U_i(\theta_0) = \int_0^\tau \left\{ V_i - \frac{S_X^{(1)}(\theta_0,t)}{S^{(0)}(\theta_0,t)} \right\} dM_i(t), \; i = 1, \ldots, n.
\]
then

$$\text{Cov}\left(n^{-1/2} \sum_{i=1}^{n} U_i(\theta_0), n^{-1/2} Q_n\right)$$

$$= \frac{1}{nE(X)} E\left(\left\{\sum_{i=1}^{n} U_i(\theta_0)\right\} \cdot \left\{\sum_{i=1}^{n} \{\bar{X}_i - X_i\}\right\} \middle| F_\tau\right)$$

$$= \frac{1}{nE(X)} E\left(\sum_{i=1}^{n} U_i(\theta_0) \cdot E\left[\sum_{i=1}^{n} \{\bar{X}_i - X_i\} \middle| F_\tau\right]\right)$$

$$= \frac{1}{nE(X)} E\left(\sum_{i=1}^{n} U_i(\theta_0) \cdot E\left[\sum_{i=1}^{n} \{\bar{X}_i - X_i\} \middle| F_\tau\right]\right)$$

$$= 0.$$ Consequently,

$$\text{Var}\left\{n^{-1/2} \hat{U}(\theta_0)\right\} = \text{Var}\left\{n^{-1/2} U(\theta_0)\right\} + \text{Var}\left(n^{-1/2} Q_n \zeta\right),$$

where

$$\text{Var}\left\{n^{-1/2} U(\theta_0)\right\} \xrightarrow{p} \Sigma$$

and

$$\text{Var}\left(\frac{1}{\sqrt{n}} Q_n \zeta\right) = \frac{\text{Var}(\bar{X}) - \text{Var}(X)}{\{E(X)\}^2} \zeta \zeta^T.$$ As a result, we have

$$\text{Var}\left\{\frac{1}{\sqrt{n}} \hat{U}(\theta_0)\right\} \xrightarrow{p} \Sigma + \frac{\text{Var}(\bar{X}) - \text{Var}(X)}{\{E(X)\}^2} \zeta \zeta^T \triangleq \Sigma + \Omega,$$

and

$$\frac{1}{\sqrt{n}} \hat{U}(\theta_0) \xrightarrow{d} N(0, \Sigma + \Omega), \quad (7)$$

where

$$\Omega = \frac{\text{Var}(\bar{X}) - \text{Var}(X)}{\{E(X)\}^2} \zeta \zeta^T.$$
Combining (6) and (7), we have

\[
\sqrt{n}(\hat{\theta} - \theta_0) = \left\{ \frac{1}{n} \frac{\partial \hat{U}(\theta^*)}{\partial \theta} \right\}^{-1} \frac{1}{\sqrt{n}} \hat{U}(\theta_0)
\]

\[\xrightarrow{d} N(0, \Sigma^{-1}(\Sigma + \Omega)\Sigma^{-1}),\]

where

\[
\Sigma^{-1}(\Sigma + \Omega)\Sigma^{-1} = \Sigma^{-1}\Sigma\Sigma^{-1} + \frac{\text{Var}(\hat{X}) - \text{Var}(X)}{(E(X))^2} \Sigma^{-1}\zeta\zeta^T\Sigma^{-1}
\]

\[= \Sigma^{-1}\Sigma\Sigma^{-1} + \frac{\text{Var}(\hat{X}) - \text{Var}(X)}{(E(X))^2} \begin{pmatrix}
0 & \cdots & 0 & 0 \\
\vdots & \ddots & \vdots & \vdots \\
0 & \cdots & 0 & 0 \\
0 & \cdots & 0 & \gamma_0^2
\end{pmatrix}.
\]

We can obtain that

\[
\sqrt{n}(\hat{\beta} - \beta_0) \xrightarrow{d} N(0, (\Sigma^{-1})_p),
\]

and

\[
\sqrt{n}(\hat{\gamma} - \gamma_0) \xrightarrow{d} N\left(0, (\Sigma^{-1})_{(p+1,p+1)} + \frac{\text{Var}(\hat{X}) - \text{Var}(X)}{(E(X))^2} \gamma_0^2\right),
\]

where \((\Sigma^{-1})_p\) and \((\Sigma^{-1})_{(p+1,p+1)}\) respectively represent the \(p\)th order sequential principal minor and the \((p + 1)\)th diagonal element of matrix \(\Sigma^{-1}\).

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