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SMIM: A unified framework of survival sensitivity analysis using multiple imputation and martingale

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Abstract

Censored survival data are common in clinical trial studies. We propose a unified framework for sensitivity analysis to censoring at random in survival data using multiple imputation and martingale, called SMIM. The proposed framework adopts the δ -adjusted and control-based models, indexed by the sensitivity parameter, entailing censoring at random and a wide collection of censoring not at random assumptions. Also, it targets a broad class of treatment effect estimands defined as functionals of treatment-specific survival functions, taking into account missing data due to censoring. Multiple imputation facilitates the use of simple full-sample estimation; however, the standard Rubin's combining rule may overestimate the variance for inference in the sensitivity analysis framework. We decompose the multiple imputation estimator into a martingale series based on the sequential construction of the estimator and propose the wild bootstrap inference by resampling the martingale series. The new bootstrap inference has a theoretical guarantee for consistency and is computationally efficient compared to the nonparametric bootstrap counterpart. We evaluate the finite-sample performance of the proposed SMIM through simulation and an application on an HIV clinical trial.

Keywords

delta adjustment; jump-to-reference; restrictive mean survival time; restrictive mean time loss; wild-bootstrap

1 | INTRODUCTION

Censored survival outcomes are common in clinical trial research of chronic diseases. Three assumptions about the censoring mechanism have been proposed: censoring completely at random (CCAR), censoring at random (CAR), and censoring not at random (CNAR). Common survival analysis methods assume CCAR and CAR that patients censored at t and patients uncensored at t with the same history have the same distribution of the entire current and future variables. This assumption will be violated if sicker subjects are more likely to

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SUPPORTING INFORMATION

Web Appendices and Tables referenced in Sections 3 and 4 and the R package for implementing the proposed methods are available with this paper at the Biometrics website on Wiley Online Library.

withdraw from the study, even after accounting for their observed history, leading to CNAR. Unfortunately, the censoring assumptions are often not testable empirically. Inappropriate assumptions may lead to biased conclusions. Regulatory agencies, such as the FDA, and the national research council (NRC, 2010) recommend sensitivity analyses to assess the robustness of study conclusions to unverifiable assumptions.

In this article, we distinguish different reasons for censoring including administrative reasons and nonadministrative reasons. For the latter, we consider patient premature dropout, which could be a case of CNAR. Many sensitivity analysis approaches have been developed for CNAR survival data. One approach is to specify a range of the residual dependence of the hazard of censoring times on the event times for the sensitivity parameter; see, for example, Rotnitzky *et al.* (2001), Scharfstein and Robins (2002), and Rotnitzky *et al.* (2007). A different approach is to directly specify pattern mixture models (Little, 1993) for event times for censored and uncensored patients and impute the missing outcomes for the censored subjects. Zhao *et al.* (2014) considered Kaplan–Meier curves to impute data, which, however, cannot include covariates. Alternatively, the δ -adjusted (Jackson *et al.*, 2014; Lipkovich *et al.*, 2016) and control-based (Lu *et al.*, 2015; Atkinson *et al.*, 2019) models are flexible to accommodate auxiliary information for sensitivity analysis of unverifiable missing data assumptions. Due to the transparency, these models have been widely used in applied research to handle missing data (e.g., NRC, 2012; Ratitch *et al.*, 2013). For generality, we consider a class of δ -adjusted/control-based Cox models for censoring due to premature dropout, indexed by sensitivity parameter δ . In δ -adjusted models, δ is a parameter comparing the outcome distribution of the subjects after nonadministrative censoring with the outcome distribution of the same subjects had they remained on study. Our framework extends readily to multiple reasons by adopting different δ 's for different groups. Control-based models assume that the event hazard for censored subjects in the active treatment group is higher (more conservative) or similar to those in the control group (Gao *et al.*, 2017). In superiority trials, the control-based models are appealing to clinical scientists since they would procedure conservative conclusions about the treatment effect if the experimental treatment is hypothesized to be better than the control treatment.

Another important question arises regarding the estimand of interest for treatment comparison in the presence of missing data. Following the International Council for Harmonization (ICH) E9 (R1) addendum, estimands should be clearly defined that describe the quantity to be estimated including how to handle intercurrent events such as premature dropout (ICH, 2019). In this article, we consider a treatment policy strategy, which evaluates treatment effect for all randomized patients on time to event endpoint regardless of the deviation of treatment such as taking rescue medication or treatment switch. When the time to event data are censored due to premature dropout, the primary analysis often assumes CAR which implicitly assumes that the hazard function for a dropout patient is the same as that for a non-dropout patient after adjusting for baseline variables included in the model. For survival sensitivity analysis using δ -adjusted models, Lipkovich *et al.* (2016) considered a marginal proportional hazards parameter, an additional structural assumption entailing a constant ratio of the hazard rates between the treatment groups. However, this parameter may be misleading (Hernán, 2010) if the proportional hazards assumption is violated as in

the δ -adjusted models. Alternatively, we consider a broad class of treatment effect estimands defined as functionals of the treatment-specific survival functions, such as the *restricted mean survival time* (RMST, Chen and Tsiatis, 2001), that is, the expectation of survival time restricted to a finite time τ . Instead of focusing on a constant hazards ratio, the RMST provides a time-evolving profile of survival times for evaluating the treatment effect, without requiring additional model assumptions.

To implement sensitivity analysis, multiple imputation (MI) is the most popular method. It consists of three steps: first, fill the missing values by plausible values to create multiple complete data sets; second, apply standard full-sample methods to analyze the multiple imputed data sets; and third, use Rubin's combining rule to summarize the results for inference. Because of its intuitive appeal, MI is recommended by the NRC as one of its preferred approaches to addressing missing data (NRC, 2012). However, many studies have realized that Rubin's variance estimator is not always consistent for general purposes (e.g., Yang and Kim, 2016). A sufficient condition for the validity of the MI inference is the congeniality condition. Roughly speaking, it requires the imputation model to be correctly specified and the subsequent analysis to be compatible with the imputation model. Even with a correctly specified imputation model, Yang and Kim (2016) showed that MI is not necessarily congenial for the method of moments estimation, so common statistical procedures may be incompatible with MI. This phenomenon becomes pronounced for adopting MI for general sensitivity analysis in clinical trials.

Lu *et al.* (2015) and Liu and Pang (2016) demonstrated that Rubin's combining rule is often conservative in control-based imputation. To overcome the conservative of Rubin's combining rule, several authors suggested the nonparametric bootstrap to obtain the standard errors (e.g., Lu *et al.*, 2015); however, the nonparametric bootstrap requires repeating imputation and analysis for all bootstrap samples and therefore causes a huge computation burden. Recently, Guan and Yang (2019) proposed the wild-bootstrap inference of a martingale representation of the MI estimator; however, their method is only applicable to continuous or binary outcomes but not censored survival outcomes. The standard nonparametric bootstrap requires resampling individual observations and repeating the imputation and analysis procedures; on the contrary, the wild-bootstrap uses an auxiliary zero-mean, unit variance random multiplier on the martingale residuals for variance estimation without re-imputation.

In this article, we propose a unified framework of survival sensitivity analysis for a class of functional estimands via MI. Specifically, the missing event times are imputed by a δ -adjusted or control-based Cox model for each treatment group. We derive a novel martingale representation of the proposed MI estimator. The martingale representation is inspired by the sequential construction of the MI estimator, namely, model parameter estimation and imputations. This new representation invokes the easy-to-implement wild-bootstrap inference with a theoretical guarantee for consistency. Moreover, unlike the nonparametric bootstrap, we do not require repeating imputation and analysis for the bootstrap resamples and therefore largely reduce the computation burden. The new SMIM (Survival sensitive analysis using *M*ultiple *I*mputation and *M*artingale) framework is fairly

flexible to accommodate a wide collection of censoring assumptions and treatment effect estimands.

2 | SETUP

2.1 | Notation and estimands

Without loss of generality, we focus on randomized clinical trials that compare a new treatment to a control treatment. We assume that the subjects constitute a random sample from a larger population. Let X_i be a vector of covariates for subject i , and let A_i be a binary treatment, 1 for the active treatment and 0 for the control treatment. Let T_i and C_i denote the time to a clinical event and the time to censoring, respectively. The full set of variables is $F_i = (X_i, A_i, T_i, C_i)$. In the presence of censoring, denote $U_i = T_i \wedge C_i$, where \wedge represents the minimum of two values, and $I_i = \mathbf{1}(T_i < C_i)$. To distinguish different reasons for censoring, denote $R_i = 1$ if censoring is due to administrative reasons and $R_i = 2$ if censoring is due to premature dropout. The observed set of variables is $O_i = \{X_i, A_i, U_i, I_i, (1 - I_i)R_i\}$. We use $O_{1:k}$ to denote the k copies $\{O_1, \dots, O_k\}$. For the total of n subjects, let $n_1 = \sum_{i=1}^n A_i$ and $n_0 = \sum_{i=1}^n (1 - A_i)$. Let the treated subjects be indexed by $i = 1, \dots, n_1$, and let the control subjects be indexed by $i = n_1 + 1, \dots, n$.

For treatment comparison, define $\lambda_a(t) = \lim_{h \rightarrow 0} h^{-1} \mathbb{P}(t \leq T < t + h \mid T \geq t, A = a)$ and $S_a(t) = \mathbb{P}(T \geq t \mid A = a)$ as the treatment-specific hazard rate and survival function at time t , respectively, for $a = 0, 1$. Under a proportional hazards assumption, one can focus on estimating the log hazard ratio $\beta = \log\{\lambda_1(t)/\lambda_0(t)\}$. However, the proportional hazards assumption may be problematic, especially when two survival curves cross. Alternatively, we focus on treatment effect estimands defined as functionals of treatment-specific survival distributions, $\tau = \Psi_\tau\{S_1(t), S_0(t)\}$ with some prespecified constant τ . This formulation covers a broad class of estimands favored in the context of nonproportional hazards; see examples of τ below.

Example 1 (Treatment effect estimands).—With a proper choice of $\Psi_\tau(\cdot)$, τ represents the following measures of treatment effect: (a) the difference in survival at a fixed time point $\tau = S_1(\tau) - S_0(\tau)$; (b) the difference of treatment-specific τ -RMSTs (restrictive mean survival times) $\tau = \mu_{1,\tau} - \mu_{0,\tau}$ where $\mu_{a,\tau} = \int_0^\tau S_a(t) dt$ for $a = 0, 1$; (c) the difference of weighted τ -RMSTs $\Delta_\tau = \int_0^\tau \omega(t)\{S_1(t) - S_0(t)\} dt$, where the nonnegative weight function $\omega(t)$ provides differentiable importance at different times; (d) the ratio of τ -RMTLs (restrictive mean time lost) $\Delta_\tau = \{\tau - \int_0^\tau S_1(t) dt\} / \{\tau - \int_0^\tau S_0(t) dt\}$; (e) the difference of τ th quantiles (e.g., medians) of survivals $\tau = q_{1,\tau} - q_{0,\tau}$ where $q_{a,\tau} = \inf_q\{S_a(q) \leq \tau\}$.

For identifiability, τ should be chosen properly. For the estimands in (a)–(d), we restrict τ to be smaller than t_{\min} , the minimum of the largest observed survival times in the two treatment groups. Similarly, for the τ th quantiles in (e), we require $\tau > \max\{S_0(t_{\min}), S_1(t_{\min})\}$.

2.2 | Simple full-sample estimator and asymptotic linearity

If the event times are fully observed, standard full-sample estimators can apply. To estimate $S_{a,\tau}(t)$, a simple estimator is the sample proportion $\hat{S}_{a,n}(t) = n_a^{-1} \sum_{i=1}^n \mathbf{1}(A_i = a) \mathbf{1}(T_i \geq t)$, for $a = 0, 1$. Then, a plug-in estimator of Δ_{τ} is $\hat{\Delta}_{\tau,n} = \Psi_{\tau}\{\hat{S}_{1,n}(t), \hat{S}_{0,n}(t)\}$.

To establish a unified framework, it is important to note that $\hat{\Delta}_{\tau,n}$ is asymptotically linear for all estimands given in Example 1. Under mild regularity conditions, we have

$$\hat{\Delta}_{\tau,n} - \Delta_{\tau} = \sum_{a=0}^1 \int_0^{\tau} \psi_a(t) \{ \hat{S}_{a,n}(t) - S_a(t) \} dt + o_p(n^{-1/2}), \tag{1}$$

for bounded variation functions $\psi_a(\cdot)$.

Lemma 1 (Asymptotic linear characterizations).—*For all estimands in Example 1, the full-sample estimators have the following asymptotic linear characterizations.*

(a) *For the difference in the survivals at a fixed time point τ , $\hat{\Delta}_{\tau,n} = \hat{S}_{1,n}(\tau) - \hat{S}_{0,n}(\tau)$, corresponding to (1) with $\psi_1(t) = -\psi_0(t) = \mathbf{1}(t = \tau)$.* (b) *For the difference of τ -RMSTs, $\hat{\Delta}_{\tau,n} = \int_0^{\tau} \{ \hat{S}_{1,n}(t) - \hat{S}_{0,n}(t) \} dt$, corresponding to (1) with $\psi_1(t) = -\psi_0(t) = 1$.* (c) *For the difference of weighted τ -RMSTs, $\hat{\Delta}_{\tau,n} = \int_0^{\tau} \omega(t) \{ \hat{S}_{1,n}(t) - \hat{S}_{0,n}(t) \} dt$, corresponding to (1) with $\psi_1(t) = -\psi_0(t) = \omega(t)$.* (d) *For the ratio of τ -RMSTs, $\hat{\Delta}_{\tau,n} = \{ \tau - \int_0^{\tau} \hat{S}_{1,n}(t) dt \} / \{ \tau - \int_0^{\tau} \hat{S}_{0,n}(t) dt \}$, corresponding to (1) with $\psi_1(t) = -\{ \tau - \int_0^{\tau} S_{0,n}(u) du \}^{-1}$ and $\psi_0(t) = -\Delta_{\tau} \{ \tau - \int_0^{\tau} S_{0,n}(u) du \}^{-1}$.* (e) *For $\Delta_{\tau} = q_{1,\tau} - q_{0,\tau}$, $\hat{\Delta}_{\tau,n} = \hat{q}_{1,\tau} - \hat{q}_{0,\tau}$, where $\hat{q}_{a,\tau} = \inf_q \{ \hat{S}_{a,n}(q) \leq \tau \}$, corresponding to (1) with $\psi_1(t) = \{ \dot{S}_1(q_{1,\tau}) \}^{-1} \mathbf{1}(t = q_{1,\tau})$ and $\psi_0(t) = -\{ \dot{S}_0(q_{0,\tau}) \}^{-1} \mathbf{1}(t = q_{0,\tau})$, where $\dot{S}_a(q) = dS_a(q)/dq$.*

2.3 | MI and the outline of the proposed SMIM framework

To facilitate applying full-sample estimators, MI proceeds as described in Table 1. It is well known that Rubin’s combining rule may overestimate the variance of the MI estimator when the full-sample estimators are not self-efficient. We provide an alternative decomposition of the MI estimator, which invokes the wild bootstrap for consistent variance estimation for general imputation models and estimands.

In Step MI-1, we consider δ -adjusted and control-based Cox imputation models for sensitivity analysis. For example, the δ -adjusted Cox model assumes the treatment-specific hazard rate of failing at time t is $\lambda_a(t | X_j)$ without premature dropout and $\delta \lambda_a(t | X_j)$ after dropout, for $a = 0, 1$.

Based on the MI with Rubin’s combining rule in Step MI-3, the variance estimator overestimates the true variance of $\hat{\Delta}_{\tau,mi}$. For rectification, we propose a wild bootstrap variance estimator (Wu, 1986) to replace Rubin’s combining rule; Theorem 2 in Section 4 shows that the proposed variance estimator is consistent for general imputation models and treatment effect estimands. The wild bootstrap procedure does not require repeating the missing data imputation step (i.e., Step MI-1) and recalculating the point estimator (i.e., Step

MI-2) using resampling data, therefore it is computationally efficient compared with the naive bootstrap.

The wild bootstrap variance estimator is motivated by a novel martingale representation of the MI estimator. Specifically, we show in Section 3 that the MI estimator of τ can be represented as $n^{1/2}(\hat{A}_{\tau, \text{mi}} - A_\tau) = \sum_{k=1}^{(1+m)n} \xi_{n,k} + o_p(1)$, where the series $\{\sum_{i=1}^k \xi_{n,i}, 1 \leq k \leq (1+m)n\}$ along with properly defined σ -fields is a martingale array. This representation invokes the wild bootstrap procedure that provides valid inference of the MI estimator of τ (Pauly, 2011).

3 | DELTA-ADJUSTED AND CONTROL-BASED MODELS

3.1 | Primary analysis with the CAR benchmark assumption

To motivate the imputation models for sensitivity analysis, we first consider a CAR assumption that $C_j \perp\!\!\!\perp T_j | (A_j, X_j)$, analogous to the missingness at random assumption (Rubin, 1976) or the coarsening at random assumption (Tsiatis, 2006). Under CAR, we have $\lambda_a(t | X_i) = \lim_{h \rightarrow 0} h^{-1} \mathbb{P}(t \leq U_i < t + h, I_i = 1 | U_i \geq t, X_i, A_i = a)$, for $a = 0, 1$. Then, we can derive $S_a(t | X_i) = \exp\{-\int_0^t \lambda_a(u | X_i) du\}$.

Following the common survival analysis literature (e.g., Chen and Tsiatis, 2001), we posit a conditional treatment-specific Cox regression with covariate X_j ; that is,

$$\lambda_a(t | X_i) = \lambda_a(t) e^{\beta_a^T X_i}, \tag{2}$$

where $\lambda_a(t)$ is an unknown baseline hazard function and β_a is a vector of unknown parameters for $a = 0, 1$. Importantly, under model (2), we do not impose the restrictive proportional hazards assumption on the treatment effect because both $\lambda_a(t)$ and β_a can be different for the two treatment groups. Let $\theta = \{\lambda_a(\cdot), \beta_a : a = 0, 1\}$ summarize the infinite-dimensional parameter in the Cox model. Under CAR, we can estimate θ from the standard software such as “coxph” in R.

We adopt the counting process framework (Andersen and Gill, 1982) to introduce the estimators and their large sample properties. Define the counting process $N_j(t) = \mathbf{1}(U_j \leq t, I_j = 1)$ of observing the event and the at-risk process $Y_j(t) = \mathbf{1}(U_j > t)$. Let $\hat{\beta}_a$ be the maximum partial likelihood estimator of β_a , for $a = 0, 1$. We can estimate $\Lambda_a(t) = \int_0^t \lambda_a(u) du$ by the Breslow (1974) estimator

$$\begin{aligned} \hat{\Lambda}_a(t) &= \int_0^t \hat{\lambda}_a(u) du, \\ \hat{\lambda}_a(u) du &= \frac{\sum_{j=1}^n \mathbf{1}(A_j = a) dN_j(u)}{\sum_{j=1}^n \mathbf{1}(A_j = a) e^{\hat{\beta}_a^T X_j} Y_j(u)}, \end{aligned}$$

and estimate $S_a(t | X_j)$ by $\hat{S}_a(t | X_i) = \exp\{-\hat{\Lambda}_a(t) e^{\hat{\beta}_a^T X_i}\}$.

3.2 | Sensitivity analyses with δ -adjusted and control-based models

CAR is not empirically testable and may be questionable for censoring due to premature dropout. We propose sensitive analysis using δ -adjusted and control-based models.

Assumption 1 (Delta-adjusted Cox model).—The treatment-specific hazard rate of failing at time t is $\lambda_a(t | X_j)$ given in (2) without premature dropout and is $\delta\lambda_a(t | X_j)$ after premature dropout ($R_j = 2$), for $a = 0, 1$, where $\delta > 0$.

It can be seen that δ quantifies the degree of the departure from the CAR assumption. If $\delta = 1$, we have CAR. If $\delta > 1$, the hazard increases after dropout, indicating a worsening of condition after dropout. If $\delta < 1$, the hazard decreases after dropout, indicating an improvement of condition after dropout. The larger the magnitude of δ , the larger the deviation from CAR. Without retrieving information for the nonadministratively censored subjects, δ cannot be ascertained. Therefore, it is recommended to vary δ in a wide range of plausible values for sensitivity analysis. To fix ideas, we use the same δ for both treatment groups, but it is easy to accommodate different δ values depending on the worsening/improvement condition for different treatment groups. For example, if the control group is a placebo group, it is reasonable to choose δ to be one for the control subjects who were nonadministratively censored. We illustrate the use of different δ for different treatment groups in Sections 5 (an application) and S7 (simulation studies).

Control-based models (e.g., Carpenter *et al.*, 2013) are another popular and appealing class of sensitivity models because of their reduced bias in favor of the experimental treatment.

Assumption 2 (Control-based Cox model).—The treatment-specific hazard rate of failing at time t is $\lambda_a(t | X_j)$ given in (2) for $a = 0, 1$ and is $\delta\lambda_0(t | X_j)$ after dropout ($R_j = 2$) for the treated, where $\delta \geq 1$.

The control-based Cox model with $\delta = 1$ becomes the jump-to-reference model (Atkinson *et al.*, 2019). It assumes that censored subjects on the active arm follow the same distribution as similar subjects in the control group after the censored time. This model is, for example, plausible for superiority trials if subjects on the control arm received the standard care, and censoring on the active arm is because subjects revert to the standard of care. For generality, we also allow δ to be less than 1, such that the treatment effect can be bracketed by the treatment effect under CAR and that for the control arm (Lu *et al.*, 2015).

In fact, censoring due to dropout can be interpreted as a time-dependent binary covariate, and δ -adjusted and control-based sensitivity models entail time-dependent Cox models. Let the history of the information up to time t be $H_j(t) = \{X_j, R_j, N_j(u), Y_j(u) : u < t\}$. Because we use $R_j = 2$ to indicate premature dropout, Assumption 1 describes the time-dependent Cox model

$$\lambda_i\{t | H_j(t); \delta, \theta\} = \lambda_i(t) \delta^{1(R_i = 2 \& t > U_i)} e^{\beta_1^T X_i}. \tag{3}$$

Assumption 2 describes the time-dependent Cox model with the hazard function, for $a = 0, 1$,

$$\lambda_a\{t \mid H_i(t); \delta, \theta\} = \begin{cases} \lambda_0(t)e^{\beta_0^\top X_i} & \text{if } a = 0, \\ \delta\lambda_0(t)e^{\beta_0^\top X_i} & \text{if } a = 1, R_i = 2, t > U_i, \\ \lambda_1(t)e^{\beta_1^\top X_i} & \text{otherwise.} \end{cases} \quad (4)$$

The *de facto* estimand for treatment policy takes into account the likely attenuation of the treatment effect after dropout. By (3) and (4), the *de facto* survival function is $S_a^{\text{sen}}(t) = \mathbb{E}[\exp\{-\int_0^t \lambda\{u \mid H_i(u); \delta, \theta\} du\}]$, for $a = 0, 1$. Here we use the superscript “sen” to denote either “ δ -adj” or “cb” for the delta-adjusted or control-based sensitivity model. The *de facto* treatment effect estimand becomes $\Delta_r^{\text{sen}} = \Psi_r\{S_1^{\text{sen}}(t), S_0^{\text{sen}}(t)\}$. If the sensitivity parameter δ is not one, Δ_r^{sen} differs from Δ_r in general. By varying δ over a certain range, Δ_r^{sen} provides valuable insights into the impact of possible departures from CAR, allowing an investigator to assess the extent to which the censoring assumption alters the treatment effect estimator.

MI requires generating the missing values from the imputation model in Step MI-1. From (3) or (4), one can derive the conditional survival function $S_a\{t \mid H_i(t); \delta, \theta\}$ for imputation. Consider the δ -adjusted model for example, if a treated subject i withdrew from the treatment, the conditional survival at $t > U_i$ is

$$S_1\{t \mid H_i(t); \delta, \theta\} = e^{-\int_{U_i}^t \delta\lambda_1(u \mid X_i) du}. \quad (5)$$

Unlike the parametric models, sampling from the semiparametric Cox model is difficult. Following Lipkovich *et al.* (2016), we introduce a general inverse transform sampling scheme. Suppose we would like to generate T_i^* from (5) for $t > U_i$. First, generate a random number u_i from $\text{Unif}[0, p_i]$, where $p_i = \{S_1(U_i \mid X_i)\}^\delta$. Second, solve $\{S_1(T_i^* \mid X_i)\}^\delta = u_i$ for T_i^* . Then, we show that given the observed data $O_{1:n}$,

$$\begin{aligned} \mathbb{P}(T_i^* \geq t \mid O_{1:n}) &= \mathbb{P}[\{S_1(T_i^* \mid X_i)\}^\delta \leq \{S_1(t \mid X_i)\}^\delta \mid O_{1:n}] \\ &= \mathbb{P}[u_i \leq \{S_1(t \mid X_i)\}^\delta \mid O_{1:n}] \\ &= \{S_1(t \mid X_i)\}^\delta / p_i = e^{-\int_{U_i}^t \delta\lambda_1(u \mid X_i) du} \end{aligned}$$

is the target imputation model (5).

In practice, we need numerical approximations to obtain T_i^* . Let $T_{a,\text{max}}$ be the largest observed event time in treatment group a for $a = 0, 1$. Because $S_a(t \mid X_i)$ is semiparametric, $\hat{S}_a(t \mid X_i)$ is only available for $t \leq T_{a,\text{max}}$. Thus we require τ to be smaller than $\tilde{T}_{\text{max}} = T_{0,\text{max}} \wedge T_{1,\text{max}}$, and then the imputed value T_i^* can be truncated at \tilde{T}_{max} .

To summarize, the MI procedure proceeds as in Table 2, where Step MI-1–3 and Step MI-1–3’ are used for δ -adjusted imputation model and control-based imputation model, respectively.

4 | WILD BOOTSTRAP INFERENCE BASED ON MARTINGALE SERIES

4.1 | A novel martingale representation

For variance estimation, the key insight is that the MI estimator is intrinsically created in a sequential manner: first, the imputation model is fitted based on the observed data; second, the missing data are drawn from the imputation model conditioned on the observed data. This conceptualization leads to a martingale representation of the MI estimator by expressing the MI estimator in terms of a series of random variables that have mean zero conditional on the sigma-algebra generated from the preceding variables. We provide heuristic steps below toward linearizing the MI estimator and forming the proper sigma-algebra and regulate details to the Web Appendix.

We first focus on treatment group $a = 1$. To unify the notation, let $T_i^{*(j)}$ denote the j th imputed value for subject i if subject i was censored and the observed T_i if we observe subject i 's event time. By the imputation mechanism, $T_i^{*(j)}$ follows the conditional survival distribution $S_1\{t | H_i(t); \hat{\theta}\}$ for $t \in U_i$, where $\theta = \{\lambda_a(\cdot), \beta_a : a = 0, 1\}$. Then, for $t \in [0, \tau]$, it is insightful to express

$$\begin{aligned} & n^{1/2} \{ \hat{S}_{1,mi}(t) - S_1^{\text{scn}}(t) \} \\ &= \frac{n^{1/2}}{mn_1} \sum_{j=1}^m \sum_{i=1}^n A_i \{ \mathbf{1}(T_i^{*(j)} \geq t) - S_1^{\text{scn}}(t) \} \\ &= \frac{n^{1/2}}{mn_1} \sum_{j=1}^m \sum_{i=1}^n A_i \{ 1 - Y_i(t) \} \\ &\times \left[\mathbf{1}(T_i^{*(j)} \geq t) - S_1\{t | H_i(t); \hat{\theta}\} \right] \end{aligned} \tag{6}$$

$$+ \frac{n^{1/2}}{n_1} \sum_{i=1}^n A_i \left[S_1\{t | H_i(t); \hat{\theta}\} - S_1^{\text{scn}}(t) \right]. \tag{7}$$

Here, we use the total sample size n for scaling; we will use the same scaling for the estimators for the control group and the treatment effect.

We analyze the two terms in (6) and (7), separately. First, because the imputations are independent given the observed data, it follows that the individual terms in (6) are independent mean-zero terms conditional on the observed data. Second, because the term in (7) depends on $\hat{\theta}$, by exploiting the counting process theory, we express

$$\begin{aligned} & \frac{n^{1/2}}{n_1} \sum_{i=1}^n A_i \left[S_1\{t | H_i(t); \hat{\theta}\} - S_1^{\text{scn}}(t) \right] \\ &= \frac{n^{1/2}}{n_1} \sum_{i=1}^n A_i \left[Y_i(t) + \{1 - Y_i(t)\}(1 - I_i) S_1\{t | H_i(t); \theta\} - S_1^{\text{scn}}(t) \right] \end{aligned} \tag{8}$$

$$+ \frac{n^{1/2}}{n_1} \sum_{i=1}^n A_i \phi_{11,i}(t) + \frac{n^{1/2}}{n_1} \sum_{i=1}^n (1 - A_i) \phi_{10,i}(t) + o_p(1), \tag{9}$$

where the exact expressions of $\phi_{11,i}(t)$ and $\phi_{10,i}(t)$ are given in Section S4. Importantly, $\phi_{11,i}(t)$ reflects the estimation of $\{\lambda_1(\cdot), \beta_1\}$, $\phi_{10,i}(t)$ reflects the estimation of $\{\lambda_0(\cdot), \beta_0\}$, and $\mathbb{E}\{\phi_{11,i}(t)\} = \mathbb{E}\{\phi_{10,i}(t)\} = 0$. Note that in the sensitivity analysis using the δ -adjusted models, the imputation for the treated group uses the information only from the treated group, so $\phi_{10,i}(t) = 0$ for all i ; while in the sensitivity analysis using the control-based models, the imputation for the treated group uses information from both treatment groups, so $\phi_{11,i}(t) = 0$ and $\phi_{10,i}(t) \neq 0$ for all i . Also, by definition, the expectation of the term in (8) is zero. Together, $n^{1/2}\{\hat{S}_{1,mi}(t) - S_1^{sen}(t)\}$ decomposes into the summation of three terms (6), (8), and (9) with (conditional) mean zero, and converges to a Gaussian process in $[0, \tau]$. Similarly, we obtain a similar asymptotic linearization of $\hat{S}_{0,mi}$ given in (S3)–(S5).

We now leverage the unified linear characterization (1) to express the MI estimator for various treatment effect estimands. Combining (1) and the above decompositions of $\hat{S}_{1,mi}(t)$ and $\hat{S}_{0,mi}(t)$, we derive

$$\begin{aligned} n^{1/2}(\hat{\Delta}_{\tau,mi} - \Delta_\tau) &= n^{1/2}[\Psi_\tau\{\hat{S}_{1,mi}(t), \hat{S}_{0,mi}(t)\} - \Delta_\tau] \\ &= \sum_{k=1}^{(1+m)n} \xi_{n,k} + o_p(1), \end{aligned} \tag{10}$$

$$\begin{aligned} \xi_{n,k} &= \frac{n^{1/2}}{n_1} \int_0^\tau \psi_1(t) A_i [\phi_{11,i}(t) + Y_i(t) \\ &+ \{1 - Y_i(t)\}(1 - I_i) S_1\{t \mid H_i(t); \theta\} - S_1^{sen}(t)] dt, \\ &\text{for } k = i(1 \leq i \leq n_1), \end{aligned} \tag{11}$$

$$\begin{aligned} \xi_{n,k} &= \frac{n^{1/2}}{mn_1} \int_0^\tau \psi_1(t) A_i \{1 - Y_i(t)\} \\ &\times [\mathbf{1}(T_i^{*(j)} \geq t) - S_1\{t \mid H_i(t); \hat{\theta}\}] dt, \\ &\text{for } k = n_1 + (i - 1)m + j(1 \leq i \leq n_1, 1 \leq j \leq m), \end{aligned} \tag{12}$$

$$\begin{aligned} \xi_{n,k} &= \frac{n^{1/2}}{n_0} \int_0^\tau \psi_0(t) (1 - A_i) [\phi_{10,i}(t) + \phi_{0,i}(t) + Y_i(t) \\ &+ \{1 - Y_i(t)\}(1 - I_i) S_0\{t \mid H_i(t); \theta\} - S_0^{sen}(t)] dt, \end{aligned} \tag{13}$$

$$\begin{aligned} &\text{for } k = (1 + m)n_1 + i, (n_1 + 1 \leq i \leq n), \\ \xi_{n,k} &= \frac{n^{1/2}}{mn_0} \int_0^\tau \psi_0(t) (1 - A_i) \{1 - Y_i(t)\} \\ &\times [\mathbf{1}(T_i^{*(j)} \geq t) - S_0\{t \mid H_i(t); \hat{\theta}\}] dt, \\ &\text{for } k = (1 + m)n_1 + n_0 + (i - 1)m \\ &+ j(n_1 + 1 \leq i \leq n, 1 \leq j \leq m). \end{aligned} \tag{14}$$

To gain intuitions, based on the decomposition in (10), the first n_1 terms of $\xi_{n,k}$ contribute to the variability of $\hat{S}_{1,mi}$ because of the unknown parameters, and the next mn_1 terms of $\xi_{n_1,k}$ contribute to the variability of $\hat{S}_{1,mi}$ because of the imputations given the estimated parameter values, reflecting the sequential MI procedure. Other terms have similar explanations.

We form the sigma-algebra $\{\mathcal{F}_{n,k}: 1 \leq k \leq (1+m)n\}$ s.t. $\mathbb{E}(\xi_{n,k} | \mathcal{F}_{n,k-1}) = 0$ for all k ; thus,

$$\left\{ \sum_{i=1}^k \xi_{n,i}, \mathcal{F}_{n,k}, 1 \leq k \leq (1+m)n \right\} \tag{15}$$

is a martingale for each $n \geq 1$.

We focus on the $\xi_{n,k}$ terms in (11) and (12) for treatment group $a = 1$, because the discussion for the $\xi_{n,k}$ terms in (13) and (14) for treatment group $a = 0$ is similar and is presented in the Web Appendix. Obviously, for $k = i(1 + n_1)$ and $\xi_{n,k}$ in (11), we have $\mathbb{E}(\xi_{n,i}) = 0$ and $\mathbb{E}(\xi_{n,k} | \mathcal{O}_{1:k-1}) = \mathbb{E}(\xi_{n,k}) = 0$, and thus we let $\mathcal{F}_{n,k} = \sigma(\mathcal{O}_1, \dots, \mathcal{O}_k)$. For $k = n_1 + (i-1)m + j$, where $i = 1, \dots, n_1$ and $j = 1, \dots, m$, and $\xi_{n,k}$ in (12), under the regularity conditions, we have $\mathbb{E}(\xi_{n,k} | \mathcal{O}_1, \dots, \mathcal{O}_{n_1}, T_1^{*(1)}, \dots, T_i^{*(j)}) = 0$, and thus we let $\mathcal{F}_{n,k} = \sigma(\mathcal{O}_1, \dots, \mathcal{O}_{n_1}, T_1^{*(1)}, \dots, T_i^{*(j)})$.

The martingale representation allows us to characterize the asymptotic distribution of $\hat{\Delta}_{\tau,mi}$ with the proof presented in Section S4.

Theorem 1.—Under Assumptions 1/2, and S1 (regularity conditions), $n^{1/2}(\hat{\Delta}_{\tau,mi} - \Delta_{\tau}) \rightarrow \mathcal{N}(0, V_{\tau,mi}^{sen})$, as $n \rightarrow \infty$, where $V_{\tau,mi}^{sen}$ is a finite variance given in (S23).

4.2 | Wild bootstrap for the MI estimator

The martingale representation invokes the wild or weighted bootstrap procedure (Wu, 1986; Liu, 1988) that provides valid variance estimation and inference of the linear statistic for martingale difference arrays. Pauly (2011) proved the validity of the wild bootstrap re-sampling under the conditions of a general central limit theorem (CLT). Guan and Yang (2019) applied the wild bootstrap for a martingale series in the context of causal inference with observational studies.

Based on the martingale representation (10), we propose the wild bootstrap procedure to estimate the variance of $\hat{\Delta}_{\tau,mi}$. The martingale representation relies on unknown quantities, requiring approximations. We then estimate (i) $S_a^{sen}(t)$ by $\hat{S}_{a,mi}$, (ii) $\phi_{11,i}(t)$, $\phi_{10,i}(t)$, and $\phi_{0,i}(t)$ by $\hat{\phi}_{11,i}(t)$, $\hat{\phi}_{10,i}(t)$, and $\hat{\phi}_{0,i}(t)$, and (iii) $S_a\{t | H_i(t); \theta\}$ by $S_a\{t | H_i(t); \hat{\theta}\}$, for $a = 0, 1$.

Based on the above approximations, the wild bootstrap inference proceeds as in Table 3.

Theorem 2 shows the asymptotic validity of the above bootstrap inference method.

Theorem 2.—Under Assumptions 1/2, and S1 (regularity conditions), we have

$$\sup_r \left| \mathbb{P}\{n^{1/2}W_L^* \leq r | \mathcal{O}_{1:n}\} - \mathbb{P}\{n^{1/2}(\hat{\Delta}_{\tau,mi} - \Delta_{\tau}^{sen}) \leq r\} \right| \rightarrow 0,$$

in probability, as $n \rightarrow \infty$.

We provide the proof of Theorem 2 in the Web Appendix, which draws on the martingale central limit theory (Hall and Heyde, 1980) and the asymptotic property of weighted sampling of martingale difference arrays (Pauly, 2011). Theorem 2 indicates that the distribution of the wild bootstrap statistic consistently estimates the distribution of the MI estimator.

5 | AN APPLICATION

We apply the proposed semiparametric δ -adjusted and control-based Cox model to an HIV clinical trial. The randomized double-blinded ACTG175 trial was conducted to compare the treatment effect of a single nucleoside and two nucleosides in adults with HIV (Hammer *et al.*, 1996). The data set is available in the R package `speff2trial`. The event of interest was the progression of the disease defined as the first occurrence of more than 50% decline in the CD4 cell count or death. For illustration purposes, we compare the treatment effect between Zidovudine monotherapy and Zidovudine plus Didanosine combination therapy in a subgroup of participants who never took any type of antiretroviral therapy before randomization. In this subgroup, there were 197 subjects in the monotherapy group and 185 subjects in the combination therapy group. There are 152 (82.2%) subjects in the Zidovudine plus Didanosine combination therapy group and 144 (73.0%) subjects in Zidovudine monotherapy group censored. We focus on estimating the RMST with the truncation time point 24 months because the ACTG175 study required at least 24 months follow-up for subjects. While re-analyzing the data, we assume CAR in the primary analysis and assume the event times follow a Cox model adjusting for age, and symptomatic indicator terms. This model assumption is assessed based on the test of the proportional hazards (Grambsch and Therneau, 1994) with a $p > 0.05$ and thus is adopted in analyses. The estimated RMST with 95% confidence interval is 22.1 (21.5, 22.8) months in the monotherapy group versus 23.0 (22.6, 23.5) in the combination therapy. The estimated between-group RMST difference with 95% confidence interval is 0.92 (0.15, 1.68). $p = 0.019$ indicates a statistically significant improvement of the combination therapy compared with the monotherapy. We also analyze the data using a direct estimator of RMST (Tian *et al.*, 2014) without imputation using the `survRM2` package. The results are close to the δ -adjusted method when $\delta = 1$, because both methods assume CAR. However, the direct estimator does not require a Cox model for missing data imputation.

We conduct the sensitivity analysis based on the δ -adjusted and control-based method to evaluate the impact of plausible departures from CAR in the primary analysis. One of the main objectives of the ACTG175 trial was to evaluate the additional benefit with the combination therapy on top of Zidovudine. Therefore, we treat the Zidovudine monotherapy group as the control group and the Zidovudine plus Didanosine combination therapy as the test treatment group. In the sensitivity analysis, we consider subjects censored before 24 months as censored for nonadministrative reasons and subjects censored after 24 months as censored for administrative reasons. For the imputation models in both δ -adjusted and control-based methods, we assume CAR for nonadministratively censored subjects in the combination therapy group or censored in the monotherapy group. In δ -adjusted method, the

δ -adjustment is applied to the primary Cox model for subjects who were nonadministratively censored in the combination therapy group. The analysis model is the resulting pattern-mixture model carried out by MI with $m = 50$. We estimate the standard errors by Rubin's combining rule and the proposed wild bootstrap method with $B = 100$.

Table 4 summarizes the results. The estimated within- and between-group standard errors from the wild bootstrap are smaller than that from Rubin's combining rule for all evaluated methods. This is coherent with the findings in the simulation study. From the p -value of each δ , the estimated tipping point of the sensitivity analysis is larger than 5 by using wild bootstrap and between 4 and 5 by using Rubin's rule. The results from the proposed wild bootstrap method demonstrate stronger evidence for the robustness of the primary analysis compared with the conservative Rubin's rule. From the sensitivity results based on the wild bootstrap, to eliminate the statistical significance of the treatment effect, the hazard of those subjects who were nonadministratively censored should be more than five times higher than subjects with the observed event times in the same group. The control-based method also provides p -values smaller than 0.05 by using both Wild Bootstrap and Rubin's rule. Therefore, the findings from the primary analysis are robust to the censoring assumption.

6 | CONCLUDING REMARKS

In this article, we provide a general framework for survival sensitivity analysis based on *semiparametric δ -adjusted and control-based Cox models* to assess the impact of plausible departures from CAR. The δ -adjusted/control-based models are flexible enough to accommodate different censoring mechanisms by changing the sensitivity parameter. MI facilitates the use of a simple full-sample estimator; however, the standard Rubin's combining rule may be conservative or anti-conservative when the analysis method is uncongenial to the imputation model (Robins and Wang, 2000). This is likely to occur in our general sensitivity analysis framework when the full-sample estimator is not an efficient estimator under the combined data and imputation models. To overcome this issue, Wang and Robins (1998) proposed consistent variance estimators for imputation estimators in the missing data literature under a parametric imputation model, which, however, is not applicable in our survival sensitivity analysis. We reformulate the MI estimator as a martingale series based on the sequential construction of the MI estimator and propose the wild bootstrap inference based on resampling the martingale series with a theoretical guarantee for consistency. The current framework considers only baseline covariates. If time-dependent covariates were available, including them makes the CAR assumption more plausible. However, the δ -adjusted and control-based models are still useful to conduct sensitivity analysis of assumptions about post-censoring behavior. Extending SMIM to incorporate time-dependent covariates will be our future work.

The proposed inferential framework targets consistent estimation of the repeated-sampling variance of the MI estimator. It appears paradoxical that the repeated-sampling variance of the MI estimator may decrease as the missingness rate increases; however, this phenomenon can happen given that the true value of the estimand changes with the missingness rate under the control-based imputation models. Alternatively, to avoid the seemingly paradoxical phenomenon, Cro *et al.* (2019) proposed a novel principle of *information anchored analysis*

in the sense that the information ratio between the analysis with missing data and the analysis with full data is similar for the primary analysis and the sensitivity analysis. Their research suggested that the control-based imputation with Rubin's variance estimate provides an information anchored analysis. In survival sensitivity analysis using control-based imputation models, Atkinson *et al.* (2019) showed by simulation that Rubin's combining rule is information-anchored.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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TABLE 1

Algorithm of multiple imputation

Step MI-1.	Create m complete data sets by filling in missing times to event with imputed values generated from an imputation model. Specifically, to create the j th imputed data set, generate $T_i^{*(j)}$ from the imputation model for each missing T_i .
Step MI-2.	Apply a full-sample estimator of τ to each imputed data set. Denote the point estimator applied to the j th imputed data set by $\hat{\Delta}_\tau^{(j)}$. Denote the variance estimator applied to the j th imputed data set by $\hat{V}^{(j)}$.
Step MI-3.	Use Rubin's combining rule to summarize the results from the multiple imputed data sets. The MI estimator of τ is $\hat{\Delta}_{\tau, \text{mi}} = m^{-1} \sum_{j=1}^m \hat{\Delta}_\tau^{(j)}$, and Rubin's variance estimator is $\hat{V}_{\text{mi}}(\hat{\Delta}_{\tau, \text{mi}}) = \frac{m+1}{(m-1)m} \sum_{j=1}^m \left(\hat{\Delta}_\tau^{(j)} - \hat{\Delta}_{\tau, \text{mi}} \right)^2 + \frac{1}{m} \sum_{j=1}^m \hat{V}^{(j)}.$

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TABLE 2

Algorithm of sensitivity analysis using δ -adjusted and control-based imputation models via multiple imputation

Step MI-1-1.	Fit a Cox model assuming CAR; denoted by $S_a(t X_i; \hat{\theta})$.
Step MI-1-2.	For administratively censored subject i with $(A_i, I_i, R_i) = (a, 0, 1)$, compute $p_i = S_a(U_i X_i; \hat{\theta})$. Draw a uniform random value $u_i \sim \text{Unif}[0, p_i]$. Impute the event time T_i^* as the solution of $u_i = S_a(t X_i; \hat{\theta})$. Numerically, we use $T_i^* = \arg \max_{t \in \mathcal{T}} \{S_a(t X_i; \hat{\theta}) \geq u_i\}$, where \mathcal{T} is the set of realized times to event or censoring with the largest value being \tilde{T}_{\max} . This will ensure that the imputed event time falls between the censoring time and \tilde{T}_{\max} .
Step MI-1-3.	For nonadministratively censored subject i with $(A_i, I_i, R_i) = (a, 0, 2)$, compute $p_i = \{S_a(U_i X_i; \hat{\theta})\}^\delta$. Draw a uniform random value $u_i \sim \text{Unif}[0, p_i]$. Impute the event time T_i^* as the solution of $u_i = \{S_a(t X_i; \hat{\theta})\}^\delta$. Numerically, we use $T_i^* = \arg \max_{t \in \mathcal{T}} [\{S_a(t X_i; \hat{\theta})\}^\delta \geq u_i]$.
Step MI-1-3'.	For nonadministratively censored subject i with $(A_i, I_i, R_i) = (0, 0, 2)$, draw T_i^* by Step MI-1-3 with $a=0$ and $\delta=1$. For nonadministratively censored subject i with $(A_i, I_i, R_i) = (1, 0, 2)$, draw T_i^* by Step MI-1-3 with $a=0$ and δ , that is, using the corresponding control distribution.

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TABLE 3

Algorithm of wild bootstrap inference based on martingale representation of the MI estimator

Step WB-1.	Sample u_k , for $k = 1, \dots, (1 + m)n$, that satisfy $\mathbb{E}(u_k O_{1:n}) = 0$, $\mathbb{E}(u_k^2 O_{1:n}) = 1$ and $\mathbb{E}(u_k^4 O_{1:n}) < \infty$.
Step WB-2.	Compute the bootstrap replicate as $W_L^* = n^{-1/2} \sum_{k=1}^{(1+m)n} \hat{\xi}_{n,k} u_k$ where $\hat{\xi}_{n,k}$ is the empirical version of $\xi_{n,k}$ by replacing the unknown quantities with their estimators and the one-dimensional integrals by the numerical integration.
Step WB-3.	Repeat Steps 1 and 2 B times, and estimate the variance of $\hat{\Delta}_{\tau, \text{mi}}$ by the sample variance of these copies of W_L^* .

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TABLE 4

Analysis of the ACTG175 trial data

Method	Zidovudine (n = 197)			Zidovudine plus Didanosine (n = 185)			Difference		
	RMST	SE	RMST	SE	RMST	SE	RMST (95% CI)	SE	p-Value
Primary and sensitivity analysis with wild bootstrap									
$\delta = 1$	22.10	0.28	23.04	0.22	0.92	0.39	(0.15, 1.68)	0.39	0.019
$\delta = 2$	22.10	0.28	23.00	0.23	0.88	0.39	(0.11, 1.64)	0.39	0.024
$\delta = 3$	22.10	0.28	22.97	0.23	0.84	0.39	(0.18, 1.61)	0.39	0.031
$\delta = 4$	22.10	0.28	22.93	0.23	0.81	0.39	(0.04, 1.58)	0.39	0.038
$\delta = 5$	22.10	0.28	22.90	0.23	0.78	0.39	(0.02, 1.55)	0.39	0.047
Control-based	22.12	0.31	23.00	0.23	0.88	0.39	(0.12, 1.65)	0.39	0.023
Primary and sensitivity analysis with Rubin's combining rule									
$\delta = 1$	22.12	0.31	23.04	0.24	0.92	0.39	(0.14, 1.69)	0.39	0.020
$\delta = 2$	22.12	0.31	23.00	0.25	0.88	0.40	(0.10, 1.67)	0.40	0.027
$\delta = 3$	22.12	0.31	22.97	0.25	0.84	0.40	(0.06, 1.63)	0.40	0.034
$\delta = 4$	22.12	0.31	22.93	0.26	0.81	0.40	(0.02, 1.60)	0.40	0.043
$\delta = 5$	22.12	0.31	22.90	0.26	0.78	0.40	(-0.01, 1.59)	0.40	0.054
Control-based	22.12	0.31	23.00	0.25	0.87	0.40	(0.08, 1.65)	0.40	0.030
(Tian <i>et al.</i> , 2014)	22.11	0.31	23.05	0.24	0.88	0.40	(0.11, 1.66)	0.40	0.026

Note: In δ -adjusted sensitivity analysis, the value of δ applied to subjects who were nonadministrative censored in the Zidovudine plus Didanosine group.