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Instrumental variable with competing risk model

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Abstract

In this paper, we discuss causal inference on the efficacy of a treatment or medication on a time-to-event outcome with competing risks. Although the treatment group can be randomized, there can be confoundings between the compliance and the outcome. Unmeasured confoundings may exist even after adjustment for measured covariates. Instrumental variable methods are commonly used to yield consistent estimations of causal parameters in the presence of unmeasured confoundings. On the basis of a semiparametric additive hazard model for the subdistribution hazard, we propose an instrumental variable estimator to yield consistent estimation of efficacy in the presence of unmeasured confoundings for competing risk settings. We derived the asymptotic properties for the proposed estimator. The estimator is shown to be well performed under finite sample size according to simulation results. We applied our method to a real transplant data example and showed that the unmeasured confoundings lead to significant bias in the estimation of the effect (about 50% attenuated).

Keywords

additive hazard model; competing risk; instrumental variable; survival analysis

1. Introduction

In clinical trials, randomization of the treatment group can only guarantee an unbiased estimation of the intent-to-treat effect. In most cases, the true efficacy of a new drug or treatment is of more interest. However, to yield a causal interpretation of the association between the drug intake/treatment and the effect, we need to remove potential confoundings between the compliance and the outcome. The assignment of treatments and the compliance to the treatments are highly dependent on the interactions between the physician and the patients. It is often hard to make all confoundings controlled by adjusting measured

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covariates. One important technique to handle the confounding issues in causal inference is the use of instrumental variables (IVs) [1], which was first introduced in econometric literatures and then applied in the field of biomedical sciences [2,3]. The concept of IV had a strong influence on causal inference studies and inspired methods such as mediation analysis [4] and Mendelian randomization [5]. By definition, an IV is a variable that is related to the exposure variable of interest but not directly linked to the outcome variable. For example, researchers used children's birthdates as an instrument to assess the effect of education on earning [6] because this variable is correlated with years of education (the exposure variable) but not directly associated with final earnings (the response).

In this paper, we are interested in estimating the efficacy of rituximab drug on diffuse large B-cell lymphoma (DLBCL) patients. The decision of whether to use the drug depends on complicated factors, and we are not able to fully control the treatment process and remove the confoundings correspondingly. Because the Food and Drug Administration (FDA) approval of rituximab affects its use frequencies in clinical practice and the calendar time is highly associated with the use of rituximab [7], we can consider the calendar time as an IV. This variable has an influence on the patients' usage of rituximab but does not change rituximab's drug effect.

In linear models, two commonly used IV estimators are two-stage least squares [8] and generalized method of moments [9]. The first method is easier to implement using the existing regression softwares, while the second is potentially more efficient when there are many instruments to use and when the model is over-identified. To use IVs in the context of time-to-event data with censoring, Robins and Tsiatis [10] proposed an IV method to handle noncompliance with the requirement that the censoring time is known (administrative censoring), which was extended to proportional hazard model by Loeys and Goetghebeur [11]. IV methods that rely on other parametric model assumptions were also proposed [12]. Recently, Li *et al.* [13] proposed an IV-based two-stage estimator for a semiparametric additive hazard model [14], and Chan [15] extended the two-stage least squares method to allow exposure-dependent censoring.

Competing risks data are commonly encountered in biomedical research. In competing risks data analysis, we are often interested in studying the covariate effects on the cumulative incidence function (CIF) of one specific cause of failure. Regression modeling, such as Cox proportional hazards model, was considered as a standard approach to model the cause-specific hazard function for each cause of failure [16–19]. It is hard to summarize the covariate effects on CIF of a particular type of failure because modeling of the cause-specific hazards would result in a complex nonlinear relationship for the CIFs. For this difficulty to be bypassed, methods that directly model the subdistribution hazard function of a specific cause were proposed [20–22]. However, there is a gap in handling confounding issues in competing risk data analysis. Scheike *et al.* [23, 24] proposed a class of flexible regression models, including multiplicative model and additive model for competing risks data through a direct binomial regression modeling approach. The idea for the construction of this model is natural, and it is easy to accommodate the model assumptions with additive model in IV analysis for the competing risks data. To fill the gap, we extend the method of

Li *et al.* [13] to the competing risks data analysis using an additive hazard subdistribution model.

In Section 2, we present our proposed model followed by detailed assumptions and estimation procedures. In Section 3, the theoretical asymptotic results are provided. In Section 4, we show extensive simulation results and discuss the performance of our proposed estimator for finite sample size compared with the simple additive hazard model fitting without using IV. In Section 5, we apply our proposed method to a real data example and compare our results with the original fitting without using IV. In Section 6, we provide more discussions of the model and its extensions. The detailed proofs can be found in the Appendix.

2. Model

2.1. Notation

Consider a competing risk study with K types of failures. Let T and C denote the failure time and the censoring time, respectively. $e \in \{1, \dots, K\}$ indicates the cause of failure. Consider right censoring; we observe a composite outcome, $T^* = \min(T, C)$ and $\delta = \mathbb{I}(T \leq C)$. Denote X_e as exposure of primary interest. Denote $X_o \in \mathbb{R}^p$ and $X_u \in \mathbb{R}^q$ as the observed and unobserved exogenous risk factors. Denote X_I as the IV. Here, we begin with one dimension of X_e and one dimension of X_I , which fits our motivation example. The general form with more predictors of interest and over-identified model are discussed in later sections. Without loss of generality, we assume that all covariates are centered at zero. Based on our notation earlier, our observed data sets are $\{T^*, \delta, \delta e, X_o, X_u, X_I\}$. Let $\mathbf{X} = \{X_e, X_o, X_u, X_I\}$; we model the cause-specific CIF as $F_1(t|\mathbf{X}) = P(T \leq t, e = 1|\mathbf{X})$ for the subgroup with covariate $\mathbf{X}$. For notation simplicity, we treat $\mathbf{X}$ as time independent. Our method can be extended to the external time-varying covariate process (i.e., interactions between time and baseline covariates) when the covariate process is available after the event occurs. We denote $N_\lambda(t) = \mathbb{I}(T_i \leq t, e_i = 1)$, $Y_\lambda(t) = 1 - N_\lambda(t)$. Because $N_\lambda(t)$ and $Y_\lambda(t)$ are not observable for all time points of censored subjects, we introduce $r_\lambda(t) = \mathbb{I}(C_i \geq T_i \wedge t)$; then both $r_\lambda(t)N_\lambda(t)$ and $r_\lambda(t)Y_\lambda(t)$ are computable for all time points.

2.2. Structural additive model for subdistribution hazard

Given the important feature that for additive hazard model, the effect is collapsible over unmeasured effects, we consider an IV analysis based on an additive subdistribution hazard model. Suppose that we are interested in cause 1; then we model the subdistribution hazard for cause 1 as

$$\lambda_1(t|\mathbf{X}) = -\frac{d}{dt} \log \{1 - F_1(t|\mathbf{X})\};$$

our model will be in the form of

$$\lambda_1(t|\mathbf{X})=h_0(t)+\beta_e X_e+\boldsymbol{\beta}_o^T \mathbf{X}_o+\boldsymbol{\beta}_u^T \mathbf{X}_u,$$

where $\beta_e \in \mathbf{R}$, $\boldsymbol{\beta}_o \in \mathbf{R}^p$, and $\boldsymbol{\beta}_u \in \mathbf{R}^q$.

Thus, we have

$$\begin{aligned} F_1(t|\mathbf{X}) &= 1 - \exp \left\{ -\int_0^t \lambda_1(s|\mathbf{X}) ds \right\} \\ &= 1 - \exp \left\{ -H_0(t) - \beta_e X_e t - \boldsymbol{\beta}_o^T \mathbf{X}_o t - \boldsymbol{\beta}_u^T \mathbf{X}_u t \right\}, \end{aligned}$$

where $H_0(t) = \int_0^t h_0(s) ds$. So

$$\begin{aligned} \lambda_1(t|X_e, \mathbf{X}_o) &= -\frac{d}{dt} \log \{1 - F_1(t|X_e, \mathbf{X}_o)\} \\ &= -\frac{d}{dt} \log [1 - E\{F_1(t|\mathbf{X})|X_e, \mathbf{X}_o\}] \\ &= -\frac{d}{dt} \log \left\{ \int \exp \left(-H_0(t) - \beta_e X_e t - \boldsymbol{\beta}_o^T \mathbf{X}_o t - \boldsymbol{\beta}_u^T \mathbf{X}_u t \right) dF(\mathbf{X}_u|X_e, \mathbf{X}_o) \right\} \\ &= -\frac{d}{dt} \log \left\{ \exp \left(-H_0(t) - \beta_e X_e t - \boldsymbol{\beta}_o^T \mathbf{X}_o t \right) \int \exp \left(-\boldsymbol{\beta}_u^T \mathbf{X}_u t \right) dF(\mathbf{X}_u|X_e, \mathbf{X}_o) \right\} \\ &= h_0(t) + \beta_e X_e + \boldsymbol{\beta}_o^T \mathbf{X}_o - \frac{d}{dt} \log \left[E \left\{ \exp \left(-\boldsymbol{\beta}_u^T \mathbf{X}_u t \right) | X_e, \mathbf{X}_o \right\} \right]. \end{aligned}$$

We assume $E(\mathbf{X}_u|X_o, X_e) = \boldsymbol{\alpha}_e X_e + \boldsymbol{\alpha}_o^T \mathbf{X}_o$ and $\text{Var}(\mathbf{X}_u|X_o, X_e) = \sigma_u^2 \mathbf{I}$, where $\boldsymbol{\alpha}_e$ is a $(q \times 1)$ -vector and $\boldsymbol{\alpha}_o^T$ is a $(q \times p)$ -matrix. Then, by second-order approximation, the aforementioned expression can be further simplified by the following approximation:

$$\tilde{h}_0(t) + \beta_e X_e + \boldsymbol{\beta}_o^T \mathbf{X}_o + \boldsymbol{\beta}_u^T (\boldsymbol{\alpha}_e X_e + \boldsymbol{\alpha}_o^T \mathbf{X}_o) = \tilde{h}_0(t) + (\beta_e + \boldsymbol{\beta}_u^T \boldsymbol{\alpha}_e) X_e + (\boldsymbol{\beta}_o + \boldsymbol{\beta}_u^T \boldsymbol{\alpha}_o^T) \mathbf{X}_o,$$

where $\tilde{h}_0(t) = h_0(t) + \beta_u^2 \sigma_u^2 t$ and $\beta_u^2 = \boldsymbol{\beta}_u^T \boldsymbol{\beta}_u$. Because $\mathbf{X}_u$ is confounding, $\boldsymbol{\alpha}_e \neq \mathbf{0}$; thus, the regression estimator for the treatment effect based on observed variables will be biased. The aforementioned approximation holds exactly when $\mathbf{X}_u = \boldsymbol{\alpha}_e X_e + \boldsymbol{\alpha}_o^T \mathbf{X}_o + \mathbf{e}_u$, with $\mathbf{e}_u$ normally distributed, and is independent of X_e and $\mathbf{X}_o$.

In order to obtain a consistent estimator of β_e , we need to use the IV X_f . Assume that X_e can be modeled as

$$X_e = \gamma_0 + \gamma_I X_I + \boldsymbol{\gamma}_o^T \mathbf{X}_o + \boldsymbol{\gamma}_u^T \mathbf{X}_u + e.$$

We present detailed assumptions required for the IV analysis in the following section. We denote $R_i(t) = r_i(t)G(t)/G(T_i \wedge t)$, $Y_i^*(t) = R_i(t)Y_i(t)$, and $N_i^*(t) = R_i(t)N_i(t)$. Denote $\hat{R}_i(t) = r_i(t)\hat{G}(t)/\hat{G}(T_i \wedge t)$, where $G(t) = P(C \geq t)$ and $\hat{G}(t)$ is estimated either from Kaplan–Meier estimator when assuming random censoring or from a specific regression model when $G_i(t) = P(C \geq t | X_{oi}, X_{fi})$ depends on X_o and X_f . For simplicity, only Kaplan–Meier estimate for the

censoring distribution is considered throughout the paper. In practice, we may consider using a stratified Kaplan–Meier estimate when the censoring distribution is dependent of some observed covariates. Denote $\hat{Y}_f(t) = \hat{R}_f(t) Y_f(t)$ and $\hat{N}_f(t) = \hat{R}_f(t) N_f(t)$. We assume that censoring distribution C is conditionally independent of (T, e) conditioning on variables X_I and X_o (assumption 6), which is stronger than a traditional assumption that C is conditionally independent of (T, e) conditioning on variables X_I , X_e , and X_o . This assumption is needed because X_e will not be included in the model for the second stage of the two-stage estimator. Other assumptions are parallel to those required for traditional additive hazard model. Thus, when assumption 6 holds, the two models' results are comparable.

Now, we propose the two-stage estimation procedure. In the first stage, we fit a model of X_e on X_I and X_o to obtain $\hat{\gamma}_0$, $\hat{\gamma}_I$ and $\hat{\gamma}_o^T$. Then compute $\hat{X}_{ei} = \hat{\gamma}_0 + \hat{\gamma}_I X_{Ii} + \hat{\gamma}_o^T X_{oi}$. In the competing risk model, we regress on $\hat{X}_{ei}$ and X_{oi} rather than X_{ei} and X_{oi} to obtain consistent estimator $\hat{\beta}_e$. For the first-stage estimator, by the result of ordinary least squares, we can estimate $\hat{\gamma} = (\hat{\gamma}_0, \hat{\gamma}_I, \hat{\gamma}_o^T)^T$ with

$$\hat{\gamma} = [X_{Io}^T X_{Io}]^{-1} [X_{Io}^T X_e],$$

where $X_{Io} = [\mathbf{1}, X_I, X_o]$ is an $n \times (p+2)$ matrix. It is obvious that $\hat{\gamma}_0$, $\hat{\gamma}_I$, $\hat{\gamma}_o^T$ are consistent estimators of γ_0 , γ_I , γ_o^T . Thus, define $\tilde{X}_e = X_{Io} \gamma$, then we have

$\hat{X}_e = X_{Io} \hat{\gamma} = X_{Io} [X_{Io}^T X_{Io}]^{-1} X_{Io}^T X_e = H_{Io} X_e$, where $H_{Io} = X_{Io} [X_{Io}^T X_{Io}]^{-1} X_{Io}^T$ is the projection matrix on X_{Io} . The ordinary linear regression result guarantees that $\hat{X}_e$ converge to $\tilde{X}_e$ uniformly in probability in a compact set of X_{Io} .

In the second stage, we fit a subdistribution additive hazard model on covariates $\hat{X}_{ei}$, X_{oi} . To fit this model, we applied the estimator proposed by Sun *et al.* [21] and used the r programming method developed by Scheike and Zhang [25]. We use estimated $\hat{X}_{ei}$ as our final estimator for β_e . To see why this works, we make the following brief derivation:

$$\begin{aligned} \lambda_1(t|\tilde{X}_{ei}, X_{oi}) &= -\frac{d}{dt} \log \left\{ 1 - F_1 \left(t|\tilde{X}_{ei}, X_{oi} \right) \right\} \\ &= -\frac{d}{dt} \log \left\{ 1 - \int F_1 \left(t|\tilde{X}_{ei}, X_{oi}, X_{ui}, e_i \right) dF \left(X_{ui}, e_i|\tilde{X}_{ei}, X_{oi} \right) \right\}. \end{aligned}$$

According to the regularity conditions (see assumptions 1, 4, and 5) and the fact that $F(X_{ui}, e_i|\tilde{X}_{ei}, X_{oi}) = F(X_{ui}, e_i|X_{Ii}, X_{oi})$, it can be further written as

$$\begin{aligned}
& -\frac{d}{dt} \log \left\{ 1 - \int F_1 \left(t | \tilde{X}_{ei}, \mathbf{X}_{oi}, \mathbf{X}_{ui}, e_i \right) dF(\mathbf{X}_{ui}, e_i | \tilde{X}_{ei}, \mathbf{X}_{oi}) \right\} \\
& = -\frac{d}{dt} \log \left[\int \exp \left\{ -H_0(t) - \beta_e \left(\tilde{X}_{ei} + \gamma_u^T \mathbf{X}_{ui} + e_i \right) t - \beta_o^T \mathbf{X}_{oi} t - \beta_u^T \mathbf{X}_{ui} t \right\} dF(\mathbf{X}_{ui}, e_i | X_{Ii}, \mathbf{X}_{oi}) \right] \\
& = -\frac{d}{dt} \log \left[\int \exp \left\{ -H_0(t) - \beta_e \tilde{X}_{ei} t - \beta_e e_i t - \beta_o^T \mathbf{X}_{oi} t - (\beta_u^T + \beta_e \gamma_u^T) \mathbf{X}_{ui} t \right\} dF(\mathbf{X}_{ui}, e_i | X_{Ii}, \mathbf{X}_{oi}) \right] \\
& = -\frac{d}{dt} \log \left[\exp \left\{ -H_0(t) - \beta_e \tilde{X}_{ei} t - \beta_o^T \mathbf{X}_{oi} t \right\} \int \exp \left\{ -\beta_e e_i t - (\beta_u^T + \beta_e \gamma_u^T) \mathbf{X}_{ui} t \right\} dF(\mathbf{X}_{ui}, e_i | X_{Ii}, \mathbf{X}_{oi}) \right] \\
& \quad = h_0^*(t) + \beta_e \tilde{X}_{ei} + \beta_o^T \mathbf{X}_{oi},
\end{aligned}$$

where $h_0^*(t) = h_0(t) - \frac{d}{dt} \log \left[\int \exp \left\{ -\beta_e e_i t - (\beta_u^T + \beta_e \gamma_u^T) \mathbf{X}_{ui} t \right\} dF(\mathbf{X}_{ui}, e_i | X_{Ii}, \mathbf{X}_{oi}) \right]$.

Under assumption 4, with second-order approximation, we have

$$\begin{aligned}
& \frac{d}{d\tilde{X}_e} \left\{ -\frac{d}{dt} \log \left[\int \exp \left\{ -\beta_e e_i t - (\beta_u^T + \beta_e \gamma_u^T) \mathbf{X}_{ui} t \right\} dF(\mathbf{X}_{ui}, e_i | X_{Ii}, \mathbf{X}_{oi}) \right] \right\} \\
& \approx \frac{d}{d\tilde{X}_e} \left[E[\gamma_u^T \mathbf{X}_u + e | X_I, \mathbf{X}_o] \beta_e + \text{Var}[\gamma_u^T \mathbf{X}_u + e | X_I, \mathbf{X}_o] \beta_e^2 t \right].
\end{aligned}$$

The approximation holds exactly when $\gamma_u^T \mathbf{X}_u + e$ follow normal distribution and the quantity on the right-hand side equal to 0 when $\gamma_u^T \mathbf{X}_u + e$ is mean 0 with constant variance, which is guaranteed by assumption 1.

Denote $\beta^T = (\beta_e, \beta_o^T)$. We have the following unbiased estimating equations:

$$\begin{aligned}
& 0 = \sum_{i=1}^n R_i(t) Y_i(t) \left\{ dR_i(t) N_i(t) - R_i(t) Y_i(t) \beta^T \left(\tilde{X}_{ei}, \mathbf{X}_{oi} \right) dt - R_i(t) Y_i(t) dH_0(t) \right\} \\
& 0 = \sum_{i=1}^n \int_0^\tau \left(\tilde{X}_{ei}, \mathbf{X}_{oi} \right) R_i(t) Y_i(t) \left\{ dR_i(t) N_i(t) - R_i(t) Y_i(t) \beta^T \left(\tilde{X}_{ei}, \mathbf{X}_{oi} \right) dt - R_i(t) Y_i(t) dH_0(t) \right\}.
\end{aligned}$$

Replace the unknown quantity $R_i(t)$ and $\tilde{X}_{ei}$ by their consistently estimated version $\hat{R}_i(t)$ and $\hat{X}_{ei}$, we can solve the following estimation equation to obtain $\hat{\beta}^T = (\hat{\beta}_e, \hat{\beta}_o^T)$. Denote

$$\mathbf{X}_{IOE} = \begin{bmatrix} \mathbf{X}_e^T \mathbf{X}_{Io} \left(\mathbf{X}_{Io}^T \mathbf{X}_{Io} \right)^{-1} \\ (0_p, 0_p, I_p) \end{bmatrix}, \text{ which is a } (p+1) \times (p+2) \text{ matrix. With known}$$

weighting function $w_i(t)$, we have

$$\begin{aligned}
& 0 = \sum_{i=1}^n w_i(t) \hat{Y}_i(t) \left\{ d\hat{N}_i(t) - \hat{Y}_i(t) \beta^T \mathbf{X}_{IOE} \mathbf{X}_{Ioi} dt - \hat{Y}_i(t) dH_0(t) \right\} \\
& 0 = \sum_{i=1}^n \int_0^\tau w_i(t) \hat{Y}_i(t) \mathbf{X}_{IOE} \mathbf{X}_{Ioi} \left\{ d\hat{N}_i(t) - \hat{Y}_i(t) \beta^T \mathbf{X}_{IOE} \mathbf{X}_{Ioi} dt - \hat{Y}_i(t) dH_0(t) \right\}.
\end{aligned}$$

From the first equation, we obtain

$$d\hat{H}_0(t) = \frac{\sum_{i=1}^n w_i(s) \hat{Y}_i(t) \left\{ d\hat{N}_i(t) - \hat{Y}_i(t) \beta^T \mathbf{X}_{IOE} \mathbf{X}_{Ioi} \right\}}{\sum_{i=1}^n w_i(t) \hat{Y}_i^2(t)}.$$

Plug the first equation solution into the second; we have

$$0 = \sum_{i=1}^n \int_0^\tau \left[\mathbf{X}_{IOE} \left\{ \mathbf{X}_{Ioi} - \frac{\sum_{j=1}^n \mathbf{X}_{Ioj} w_j(t) \hat{Y}_j^2(t)}{\sum_{j=1}^n w_j(t) \hat{Y}_j^2(t)} \right\} \right] \times w_i(t) \hat{Y}_i(t) \left\{ d\hat{N}_i(t) - \hat{Y}_i(t) \boldsymbol{\beta}^T \mathbf{X}_{IOE} \mathbf{X}_{Ioi} dt \right\}.$$

So we have

$$\begin{aligned} \hat{\boldsymbol{\beta}} &= \left(n^{-1} \sum_{i=1}^n \int_0^\tau \left[\mathbf{X}_{IOE} \left\{ \mathbf{X}_{Ioi} - \frac{\sum_{j=1}^n \mathbf{X}_{Ioj} w_j(t) \hat{Y}_j^2(t)}{\sum_{j=1}^n w_j(t) \hat{Y}_j^2(t)} \right\} \right]^{\otimes 2} w_i(t) \hat{Y}_i^2(t) dt \right)^{-1} \times \left(n^{-1} \sum_{i=1}^n \int_0^\tau \left[\mathbf{X}_{IOE} \left\{ \mathbf{X}_{Ioi} - \frac{\sum_{j=1}^n \mathbf{X}_{Ioj} w_j(t) \hat{Y}_j^2(t)}{\sum_{j=1}^n w_j(t) \hat{Y}_j^2(t)} \right\} \right] w_i(t) \right) \\ &= \mathbf{S}_{2n}^{-1}(\hat{\boldsymbol{\gamma}}, \hat{\Lambda}_c) \mathbf{S}_{1n}(\hat{\boldsymbol{\gamma}}, \hat{\Lambda}_c), \end{aligned}$$

where $a^{\otimes 2} = aa^T$.

The baseline hazard is not identifiable because of the confounding of $\mathbf{X}_u$; that is, we can estimate $H_0^*(t) = \int_0^t h_0^*(s) ds$, but we are not able to estimate $H_0(t)$. However, we are still able to estimate covariate-specific subdistribution cumulative incident function because it can be represented by $h_0^*(t)$ instead of $h_0(t)$; then we have

$F_1(t|X_e, \mathbf{X}_o) = 1 - \exp \left(-H_0^*(t) - t\beta_e X_e - t\boldsymbol{\beta}_o^T \mathbf{X}_o \right)$. We can obtain

$F_1(t|X_e, \mathbf{X}_o) = 1 - \exp \left(-\hat{H}_0^*(t) - t\hat{\beta}_e X_e - t\hat{\boldsymbol{\beta}}_o^T \mathbf{X}_o \right)$ with

$$\hat{H}_0^*(t) = \int_0^t \frac{\sum_{i=1}^n w_i(s) \hat{Y}_i(s) \left\{ d\hat{N}_i(s) - \hat{Y}_i(s) \hat{\boldsymbol{\beta}}^T \mathbf{X}_{IOE} \mathbf{X}_{Ioi} ds \right\}}{\sum_{i=1}^n w_i(s) \hat{Y}_i^2(s)}.$$

To handle the technical difficulty of additive model that the estimated hazard might not be positive, we use the approach as suggested for the original additive model [14] by defining a modified version of estimation $\hat{H}_{mod}^*(t) = \max_{0 \leq s \leq t} \hat{H}_0^*(s)$. Under regularity condition, this modified version of $\hat{H}_{mod}^*(t)$ is asymptotically equivalent to $\hat{H}_0^*(t)$ and thus, we proof the asymptotics results for $\hat{H}_0^*(t)$.

3. Theoretical results

We assume that the following regularity conditions hold throughout the paper.

Assumption 1— X_I , X_u , and X_o are mean zero random variables. $\boldsymbol{\gamma}_u^T \mathbf{X}_u + e$ is uncorrelated with X_o and X_I , that is, $E \left(\boldsymbol{\gamma}_u^T \mathbf{X}_u + e | X_o, X_I \right) = 0$. The variance is constant, that is, $\text{Var} \left(\boldsymbol{\gamma}_u^T \mathbf{X}_u + e | X_o, X_I \right) = \sigma^2$.

Assumption 2—The IV X_I is associated with X_e conditional on X_o and X_u , that is, $\alpha_I \neq 0$.

Assumption 3— X_I is not directly associated with the outcome event; that is, X_I is independent of (T, e, X_u) conditional on X_o .

Assumption 4—The error term e has mean 0. e is independent of X_I , X_o , and X_u .

Assumption 5— X_o and X_u are independent.

The assumptions earlier are parallel to the traditional IV assumptions, with the uncorrelated assumption replaced by independence assumption because our model is nonlinear. Because we are considering the additive hazard subdistribution model, we also need the following assumptions related to the additive hazard model.

Assumption 6—Independent censoring, that is, C being conditionally independent of (T, e) , conditional on variables X_I and X_o .

Assumption 7—Covariates X_o , X_I , X_u , X_e have bounded supports, and β is an interior point of the possible parameter space.

Assumption 8—When the time period of interest is $[0, \tau]$, we require $P(C \neq 0 | X_o, X_I)$ to be bounded away from 0 for $t \in [0, \tau]$.

Assumption 9— $n^{-1} \sum_{i=1}^n \int_0^\tau \left[X_{IOE} \left\{ X_{Ioi} - \frac{\sum_{j=1}^n X_{Ioj} w_j(t) Y_j^{*2}(t)}{\sum_{j=1}^n w_j(t) Y_j^{*2}(t)} \right\} \right]^{\otimes 2} w_i(t) Y_i^{*2}(t) dt$ converge uniformly with probability 1 to a positive definite matrix process Ω_τ .

Assumption 10—

$n^{-1} \sum_{i=1}^n \int_0^\tau \left[X_{IOE} \left\{ X_{Ioi} - \frac{\sum_{j=1}^n X_{Ioj} w_j(t) Y_j^{*2}(t)}{\sum_{j=1}^n w_j(t) Y_j^{*2}(t)} \right\} \right]^{\otimes 2} w_i(t) Y_i^{*2}(t) dN_i^*(t)$ converges uniformly with probability 1 to a positive definite matrix process Ψ_τ .

Assumption 11—

$$\begin{aligned} & \frac{\sigma^2 \beta_{0e}^2}{n} \sum_{i=1}^n \int_0^\tau X_{IOE} \left[X_{Ioi} - \left\{ \frac{\sum_{j=1}^n X_{Ioj} w_j(t) Y_j^{*2}(t)}{\sum_{j=1}^n w_j(t) Y_j^{*2}(t)} \right\} \right] \\ & X_{Ioi}^T \left(X_{Io}^T X_{Io} \right)^{-1} X_{Ioi} \\ & \times \left[X_{IOE} \left\{ X_{Ioi} - \frac{\sum_{j=1}^n X_{Ioj} w_j(t) Y_j^{*2}(t)}{\sum_{j=1}^n w_j(t) Y_j^{*2}(t)} \right\} \right]^T w_i(t) Y_i^{*2}(t) dt \end{aligned}$$

converges uniformly with probability 1 to a positive definite matrix process Σ_τ .

Assumption 12—For $\tau < \infty$, there exist bounded continuous functions $g(t)$ and $\Gamma(t)$ such that

$$\left\| \int_0^t \frac{n^{-1} \sum_{i=1}^n w_i^2(s) Y_i^{*2}(s) dN_i^*(s)}{[n^{-1} \sum_{i=1}^n w_i(s) Y_i^{*2}(s)]^2} - g(t) \right\|_{\infty}$$

and

$$\left\| \int_0^t \mathbf{X}_{IOE} \frac{\sum_{j=1}^n \mathbf{X}_{IOj} w_j(s) Y_j^*(s) dN_j^*(s)}{\sum_{j=1}^n w_j(s) Y_j^{*2}(s)} - \Gamma(t) \right\|_{\infty}$$

converge to 0 in probability uniformly over $t \in (0, \tau]$.

We provide theoretical results in this section with brief proof outline. The technical details of the proofs can be found in the Appendix.

Theorem 1—Under assumptions 1–11, $\hat{\beta}$ converges to β_0 with probability 1.

Proof: Because $\hat{\gamma}$ and $\hat{\Lambda}_c$ converge to γ and Λ_c uniformly and the regularity conditions ensure that the function space is in Glivenko–Cantelli class, we have that

$\hat{\beta} = S_{2n}^{-1}(\hat{\gamma}, \hat{\Lambda}_c) S_{1n}(\hat{\gamma}, \hat{\Lambda}_c)$ converges to $\tilde{\beta} = S_{2n}^{-1}(\gamma, \Lambda_c) S_{1n}(\gamma, \Lambda_c)$ uniformly with probability 1. By the convergence result for the additive subdistribution hazard model, we know that $\tilde{\beta}$ converges to β_0 with probability 1. Thus, $\hat{\beta}$ converges to β_0 with probability 1.

For simplicity of the variance form, we will choose Kaplan–Meier estimator for $\hat{G}(t)$ and assume random censoring. In practice, if we believe that censoring depends on X_o and X_f , we can model it via certain semiparametric models. Under the correct specification of such models, the consistency and asymptotic normality results still hold, although the variance will have a more complicated form and the Bootstrap will be recommended for.

Theorem 2—Under assumptions 1–11, we have

$$\sqrt{n}(\hat{\beta} - \beta_0) \rightarrow_d N(0, \Omega_{\tau}^{-1}(\Psi_{\tau} + \sum_{\tau}) \Omega_{\tau}^{-1})$$

with influence function Φ_j as defined in the Appendix. The variance can be estimated by using an empirical version of $\hat{\Phi}_j$ of Φ_j and compute $n^{-1} \sum_{i=1}^n \Phi_i^{\otimes 2}$ to estimate $E\Phi_i^{\otimes 2}$. See the Appendix for a detailed expression of influence function Φ_j .

Theorem 3—Under assumptions 1–12, we have

$$\sup_{t \in (0, \tau]} |\hat{F}_1(t|x_e, \mathbf{x}_o) - F_1(t|x_e, \mathbf{x}_o)| \rightarrow_p 0,$$

and $\sqrt{n}(\hat{F}_1(t|x_e, \mathbf{x}_o) - F_1(t|x_e, \mathbf{x}_o))$ converges weakly to a mean zero Gaussian process with covariance matrix

$$K(s, t) = (1 - F_1(t|x_e, \mathbf{x}_o))(1 - F_1(s|x_e, \mathbf{x}_o)) [g(t \wedge s) + ts(x_e, \mathbf{x}_o)\Omega_\tau^{-1}(\Psi_\tau + \sum_\tau)\Omega_\tau^{-1}(x_e, \mathbf{x}_o)^T + (x_e, \mathbf{x}_o)\Omega_\tau^{-1}(\Gamma(t)s + \Gamma(s)t)].$$

4. Simulation

We randomly sample X_I from $\{0, 1\}$ with equal probability. X_o and X_u are sampled from independent standard normal distributions. X_e is generated as $X_e = (1, X_I, X_o, X_u)\boldsymbol{\gamma}^T$ with $\boldsymbol{\gamma} = (0, \gamma_2, 0.5, -1)$. By changing γ_2 from 0.2 to 0.4, we mimic the setting with weak and strong IVs. We vary the sample size $n = 100, 400, 1000$. Let $t_0 = 0.6$ be a fixed time point and denote $t^* = \min(t, t_0)$. We simulate event time data from the following subdistribution rate:

$$\begin{aligned} F(t, \varepsilon=1) &= 1 - \{1 - p(1 - e^{-t})\} \exp\{-\beta_e X_e t - \beta_o X_o t - \beta_u X_u t\}, \\ F(t, \varepsilon=2) &= \frac{(1-p)(1 - e^{-t}) \exp\{-\beta_e X_e t^* - \beta_o X_o t^* - \beta_u X_u t^*\}}{\exp\{-\beta_e X_e t_0 - \beta_o X_o t_0 - \beta_u X_u t_0\}}. \end{aligned}$$

In this way, we guarantee that $P(\varepsilon = 1) = p$ and $P(\varepsilon = 2) = 1 - p$ have a sum $F(\infty, \varepsilon = 1) + F(\infty, \varepsilon = 2) = 1$ and both $F(t, \varepsilon = 1)$ and $F(t, \varepsilon = 2)$ are increasing functions. We first generate ε and then generate T_1 and T_2 given ε by

$$\begin{aligned} F(t|\varepsilon=1) &= \frac{1 - \{1 - p(1 - e^{-t})\} \exp\{-\beta_e X_e t^* - \beta_o X_o t^* - \beta_u X_u t^*\}}{1 - (1-p) \exp\{-\beta_e X_e t_0 - \beta_o X_o t_0 - \beta_u X_u t_0\}}, \\ F(t|\varepsilon=2) &= \frac{\exp\{-\beta_e X_e t^* - \beta_o X_o t^* - \beta_u X_u t^*\}}{\exp\{-\beta_e X_e t_0 - \beta_o X_o t_0 - \beta_u X_u t_0\}}. \end{aligned}$$

We set censoring time as exponentially distributed with parameters set to make 30% and 50% censoring rate. We set $p = 0.8$, $\boldsymbol{\beta} = (0.5, 0.2, \beta_3)$. When setting $\beta_3 = 0$, we have the case of no unmeasured confoundings. When setting $\beta_3 = 0.2$ and 0.4, we have the cases with weak and strong unmeasured confoundings. The results are summarized in Table I.

From the results, we can see that when IV is strong, the IV method has small bias and correct coverage rate for its 95% nominal confidence interval. However, when IV becomes weak, the IV estimator performance becomes unsatisfactory, especially in the small sample size case (i.e., $n = 100$). When IV assumption does not hold and the IV is independent of the exposure, the IV method fails (with very large bias and variance) as we expected. When IV is strong, we compare the IV method and the traditional regression method. When there are no unmeasured confoundings, both methods yield small bias and correct coverage rates for their 95% nominal confidence interval, although the IV estimator is not as efficient as a regression-based estimator. However, as confounding effects increase, we observe the dramatic increase of bias and a smaller coverage rate for regression method, while the IV estimator still maintains small bias and the standard error increases very slightly. The coverage rate is approximately at its nominal level.

In practice, we recommend checking first whether the IV is strong or not by looking at some ad hoc statistics from first-stage regression model. For example, the F-statistics >10 is often used in econometric literature [26] as a criteria for strong IV, when an IV is not very strong while the confounding might be small. The balance-variance trade-off might favorate using traditional regression method. So we recommend running both models and compare the results. If the two estimators are very different, then we can see bias in traditional regression method and IV estimator shall be used. If there is no significant difference between the two, then the traditional regression results could be used, while the IV results can be considered as sensitivity analysis.

5. Real transplant data example

We now apply the proposed IV analysis method to a real data example. We considered data from the Center for International Blood and Marrow Transplant Research (CIBMTR), on 994 DLBCL patients, who are 18 to 76 years old and had an autologous hematopoietic stem cell transplantation (TX) between 1996 and 2003 [7]. The CIBMTR comprised clinical and basic scientists who share data on their blood and bone marrow transplant patients, with the CIBMTR Data Collection Center located at the Medical College of Wisconsin. The CIBMTR has a repository of information regarding the results of transplants at more than 450 transplant centers worldwide. The specific aim of the study was to compare the clinical outcomes whether rituximab was (+R cohort, $n = 176$) or was not (−R cohort, $n = 818$) administered as therapy prior to the transplant. The clinical outcomes compared include relapse/progression of DLBCL, non-relapse mortality (NRM; defined as death without relapse/progression), progression-free survival and overall survival. Here, relapse/progression and NRM are two competing risks. A total of 355 patients were censored at the end of the study, and censoring distribution is independent of all adjusted covariates by fitting a Cox model for the censoring distribution including all adjusted covariates ($p > 0.10$ for each covariate). The CIBMTR study treated the year of TX (2000–2003 vs 1996–1999) as a regular covariate that needs to be adjusted if it is significant in the regression mode, and concluded that pre-TX rituximab did not affect NRM (hazard ratio (HR) = 0.70, $p = 0.18$) with year of TX to be included in the model (HR = 0.63, $p = 0.05$). The risk of relapse/progression was lower in the +R cohort compared with the −R cohort (HR = 0.67, $p = 0.004$) without year of TX to be included in the final model because it was not significant (HR = 0.86, $p = 0.25$).

In the CIBMTR study cohort, there were 18% (174/986) patients who received rituximab in pre-transplant therapy and only 1% (6/482) had rituximab among those transplanted prior to 1999. Calendar time (year of TX) was highly associated with the use of rituximab because the increase in the use of rituximab was a result of approval by the US FDA in 1998. Prior to 1998, rituximab was available only in clinical trials. Thus, including calendar time (year of TX) as a regular covariate in a regression analysis could lead to a biased conclusion because we cannot estimate the true effect of rituximab in the presence of year of TX. Besides the observed adjusted covariates [7], there exist some unobserved covariates, such as molecular subtype of lymphoma (e.g., germinal center versus activated B-cell versus double-hit lymphoma) [27]. These additional prognostic covariates were unknown at the time that these patients were treated and the analysis was carried out. Such unobserved covariates may

affect clinical outcomes and may be imbalanced between the +R and -R cohorts. In the setting of autologous transplantation, transplant-related mortality is low (<3% at 1 year) and there were no major technical improvements during this short time period. Also, there were no major clinical practice changes over this short study time period that would have had an impact on transplant in lymphoma except the FDA approval of rituximab. So it is reasonable to assume that the calendar time over such short study time period will not be associated with any of potential unmeasured confounding variables. We use Year of TX (before or after the FDA approval the drug) as an IV in proposed IV additive regression model to analyze competing risks data. Risk factors adjusted were age, disease status, and number of lines of chemotherapy for relapse/progression and were age, time from diagnosis (DX) to TX, and Karnofsky score for NRM. The analysis results for fitting a regular regression including year of TX (model 1), without year of TX (model 2), and IV regression analysis (model 3) are given in Table II. When year of TX was incorrectly included in the regression models, pre-transplant rituximab did not affect both relapse/progression and NRM because part of the drug effects were counted by the artificial effect of calendar time of year of TX. Without adjusting year of TX, estimated rituximab effects were underestimated, where estimated effect size of rituximab by regular regression compared with IV analysis were increased from -0.0043 to -0.0104 (relatively, 1.42 times increasing) for relapse/progression and increased from -0.0017 to -0.0049 (relatively, 1.88 times increasing) for NRM. Increasing in the size of rituximab effect on the CIF can be seen in the plot of predicted CIF for +R cohort versus -R cohort. At 72 months since TX, the rituximab effect in CIF of relapse/progression were 20% and 7% by IV regression analysis and by regular regression analysis, respectively (Figure 1). Similarly, the rituximab effect in CIF of NRM was 23% and 8% by IV regression analysis and by regular regression analysis, respectively (Figure 2). We observe significant increase in rituximab effect by IV regression modeling. We performed a goodness-of-fit test to check whether all covariates have constant effect [28]. The test indicates that the main treatment effect has a constant effect ($p > 0.1$) and 'disease status' and 'prior lines of therapy' have time-varying effects for relapse, while for NRM, the main treatment effect has a constant effect and 'time from DX to TX', 'Karnofsky score', and 'missingness of Karnofsky score' have time-varying effects. We considered fitting more flexible model, allowing time-varying effects for covariates that failed the constant effect test. Both models give almost identical results for the main effect (<1% difference in estimation). Thus, for the illustration purpose, we present all results based on constant effect additive model. Another limitation of the current analysis is that the exposure is binary, while the method requires us to fit a linear model of it.

To check whether the linear model approximately holds, we check the interaction between the binary IV and other covariates and did not notice strong interaction; also, we performed simulation analysis to check how bias the result could be if the true model is logistic. From Table S1, we could see that the nonidentity link could lead to some bias in the estimator; however, it tends to also increase the variability, and the coverage rate is still reasonable.

With calendar time of before or after the FDA approval of rituximab (year of TX) as an IV, we confirmed rituximab effect on both relapse/progression and NRM. In conclusion, it is important to identify IV and to model and analyze the IV appropriately in regression analyses.

6. Discussion

Only Kaplan–Meier estimate for the censoring distribution is considered throughout the paper, which requires a strong assumption that censoring time C is independent of observed covariates. It is clear that this may not be true. He *et al.* [29] showed that using covariate-adjusted censoring weight can reduce the bias and improve the efficiency in fitting a proportional subdistribution hazards model when the censoring distribution is dependent of some covariates. Thus, it is useful to generalize the proposed methods and study the performance by using a regression model for the censoring distribution.

When the exposure is non-Gaussian and generalized linear model instead of linear model holds for the exposure model, the mean–variance relationship will cause that the variance of $\gamma_u^T X_u + e$ depends on X_I and X_o and thus on $\tilde{X}_e$ and introduces potential bias depending on the degree of nonlinearity. When the mean condition holds while the variance condition not, we will have bias in the second-stage estimator from the second-order approximation. However, if the variance is not very sensitive to the mean or the range of mean is small, the term is still approximately uncorrelated to $\tilde{X}_e$, and thus, the bias is small, for example, in our real data example.

In this paper, we proposed consistent estimators of efficacy of treatment in the presence of unmeasured confoundings. We showed the asymptotic results of these estimators and studied their performance under finite sample size using simulation. The data example shows that by adjusting unmeasured confounding using IV, we are able to identify stronger treatment effects. One limitation of this method is that because of the nature of additive models, in certain cases it is hard to guarantee the subdistribution hazard to be positive. Although it is quite clear in our example that the approval from FDA will not directly affect the survival outcome, finding a valid IV may be challenging in some other settings. The sensitivity analysis is required if we are not sure whether the exclusion restriction assumption holds.

Although we assume time-independent effects in our model, the method can be straightforwardly extended to allow time-varying effects $\beta(t)$ for the two-stage estimator with a more complicated theoretical variance form. In general, we can replace the two-stage approach by the following one-stage approach:

$$0 = E[I(T > t, \varepsilon = 1) \exp\{-\beta^T(t)(X_e, X_o)\}(X_I - EX_I | X_o)].$$

Because $I(T > t, \varepsilon = 1)$ is not always observable because of the censoring, we can use the Inverse Probability Censoring Weighting (IPCW) method with weights derived in Zhang *et al.* [30]. The estimating equation can be written as

$$0 = E[R(t)I(T > t, \varepsilon = 1) \exp\{-\beta^T(t)(X_e, X_o)\}(X_I - EX_I | X_o)].$$

This allows weaker assumptions (i.e., uncorrelated assumption rather than independence assumption for X_I and outcome conditional on X_e, X_o) and more efficient results. On the

other hand, the advantage of the two-stage approach is computational, and it is easy to be implemented using current available software.

In conclusion, the two-stage least squares estimator is a useful method to handle unmeasured confounding variables for competing risk data analysis, and it has good finite sample size and asymptotic performance. The two-stage approach is easy to implement using available software and can be used in various settings including time-varying effect and time-varying covariate X_{ϕ} . The design of measuring useful instrument variable shall provide us better understanding of the treatment effect under potential confounding for compliance.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix

A.1. Proof of Theorem 1

We first study the behavior of $S_{1n}(\hat{\gamma}, \hat{\Lambda}_c)$. We denote $\tilde{X}_i = (\tilde{X}_{ci}, X_{oi})$ and $\hat{X}_i = (\hat{X}_{ci}, X_{oi})$.

Denote $M_i^*(t) = N_i^*(t) - \int_0^t Y_i^* dH_i(t)$ as an square integrable martingale. We can rewrite $S_{1n}(\hat{\gamma}, \hat{\Lambda}_c)$ as

$$\begin{aligned}
 S_{1n}(\hat{\gamma}, \hat{\Lambda}_c) &= n^{-1} \sum_{i=1}^n \int_0^\tau \left[\hat{X}_i^T - \frac{\sum_{j=1}^n \hat{X}_j^T w_j(t) \hat{Y}_j^2(t)}{\sum_{j=1}^n w_j(t) \hat{Y}_j^2(t)} \right] w_i(t) \hat{Y}_i(t) d\hat{N}_i(t) \\
 &= n^{-1} \sum_{i=1}^n \int_0^\tau \left[\hat{X}_i^T - \frac{\sum_{j=1}^n \hat{X}_j^T w_j(t) \hat{Y}_j^2(t)}{\sum_{j=1}^n w_j(t) \hat{Y}_j^2(t)} \right] w_i(t) \hat{Y}_i(t) dM_i^*(t) + n^{-1} \sum_{i=1}^n \int_0^\tau \left[\hat{X}_i^T - \frac{\sum_{j=1}^n \hat{X}_j^T w_j(t) \hat{Y}_j^2(t)}{\sum_{j=1}^n w_j(t) \hat{Y}_j^2(t)} \right] w_i(t) \hat{Y}_i(t) (\hat{R}_i(t) - R_i(t)) dN_i(t) \\
 &= S_{11n} + S_{12n}.
 \end{aligned}$$

For Kaplan–Meier estimator, we have

$$\hat{R}_i(t) - R_i(t) = -\frac{G(t)I(T_i \leq t)}{G(T_i)} \sum_{j=1}^n \int_{T_i}^t \frac{dM_j^c(u)}{\sum_{k=1}^n I(T_k \geq u)},$$

where $M_j^c(u) = I(T_i \leq u, \varepsilon_i = 0) - \int_0^u I(T_i \geq t) d\Lambda^c(t)$. Because of the consistency of $\hat{\gamma}$ and the uniform convergence of $\hat{G}(\cdot)$, we have

$$S_{12n} = n^{-1} \sum_{i=1}^n \int_0^\tau \left[\tilde{\mathbf{X}}_i^T - \frac{\sum_{j=1}^n \tilde{\mathbf{X}}_j^T w_j(t) Y_j^{*2}(t)}{\sum_{j=1}^n w_j(t) Y_j^{*2}(t)} \right] w_i(t) Y_i^*(t) (\hat{R}_i(t) - R_i(t)) dN_i(t) + o_p(1).$$

So we have that S_{12n} is an average of martingale integrals with respect to the censoring filtration $\mathcal{F}(u) = \{I(T_i \leq u, \varepsilon_i = 0), I(T_i \leq t), \mathbf{X}_i, i = 1, \dots, n, t \leq u\}$. Under regularity condition, this term is dominated by a bounded function and converges in probability to 0 uniformly in a compact neighborhood of β_0 [31]. Because of the consistency of $\hat{\gamma}$ and uniform convergence of $\hat{G}(\cdot)$, we also have

$$\left[\hat{\mathbf{X}}_i^T - \frac{\sum_{j=1}^n \hat{\mathbf{X}}_j^T w_j(t) \hat{Y}_j^2(t)}{\sum_{j=1}^n w_j(t) \hat{Y}_j^2(t)} \right] w_i(t) \hat{Y}_i(t) = \left[\tilde{\mathbf{X}}_i^T - \frac{\sum_{j=1}^n \tilde{\mathbf{X}}_j^T w_j(t) Y_j^{*2}(t)}{\sum_{j=1}^n w_j(t) Y_j^{*2}(t)} \right] w_i(t) Y_i^*(t) + o_p(1).$$

So we have

$$S_{11n} = n^{-1} \sum_{i=1}^n \int_0^\tau \left[\tilde{\mathbf{X}}_i^T - \frac{\sum_{j=1}^n \tilde{\mathbf{X}}_j^T w_j(t) Y_j^{*2}(t)}{\sum_{j=1}^n w_j(t) Y_j^{*2}(t)} \right] w_i(t) Y_i^*(t) dM_i^*(t) + o_p(1).$$

Because of the consistency of $\hat{\gamma}$ and the uniform convergence of $\hat{G}(\cdot)$, we can approximate $S_{2n}(\hat{\gamma}, \hat{\Lambda}_c)$ by

$$S_{2n}(\hat{\gamma}, \hat{\Lambda}_c) = n^{-1} \sum_{i=1}^n \int_0^\tau \left[\tilde{\mathbf{X}}_i^T - \frac{\sum_{j=1}^n \tilde{\mathbf{X}}_j^T w_j(t) Y_j^{*2}(t)}{\sum_{j=1}^n w_j(t) Y_j^{*2}(t)} \right]^{\otimes 2} w_i(t) Y_i^{*2}(t) dt + o_p(1).$$

Based on the consistency results for traditional additive competing risk model without IV, $\tilde{\beta} = S_{2n}(\gamma, \Lambda_c)^{-1} S_{1n}(\gamma, \Lambda_c)$ converge to β_0 . Because we have shown that our estimator $\hat{\beta} - \tilde{\beta} = o_p(1)$, so we obtain the consistency for $\hat{\beta}$.

A.2. Proof of Theorem 2

Denote $U_n(\boldsymbol{\beta}) = S_{2n}\boldsymbol{\beta} - S_{1n}$; we have S_{2n} converge to positive definite matrix Ω_{τ} . To obtain distribution of $\hat{\boldsymbol{\beta}}$, we know

$$\sqrt{n}(\hat{\boldsymbol{\beta}} - \boldsymbol{\beta}_0) = A_{\tau}^{-1} \sqrt{n}U_n(\boldsymbol{\beta}_0) + o_p(1).$$

So we just need to provide an expansion of $\sqrt{n}U_n(\boldsymbol{\beta}_0)$. We have

$$\begin{aligned} & \sqrt{n}U_n(\boldsymbol{\beta}_0) \\ = & n^{-1/2} \sum_{i=1}^n \int_0^{\tau} \left[\mathbf{X}_{IOE} \left(\mathbf{X}_{Ioi} - \frac{\sum_{j=1}^n \mathbf{X}_{Ioj} w_j(t) \hat{Y}_j^2(t)}{\sum_{j=1}^n w_j(t) \hat{Y}_j^2(t)} \right) \right] w_i(t) \hat{Y}_i(t) [d\hat{N}_i(t) - \hat{Y}_i(t) \boldsymbol{\beta}_0^T \mathbf{X}_{IOE} \mathbf{X}_{Ioi} dt] \\ & = n^{-1/2} \sum_{i=1}^n \int_0^{\tau} \left[\mathbf{X}_{IOE} \left(\mathbf{X}_{Ioi} - \frac{\sum_{j=1}^n \mathbf{X}_{Ioj} w_j(t) \hat{Y}_j^2(t)}{\sum_{j=1}^n w_j(t) \hat{Y}_j^2(t)} \right) \right] w_i(t) \hat{Y}_i(t) dM_i^*(t) \\ & \quad + n^{-1/2} \sum_{i=1}^n \int_0^{\tau} \left[\mathbf{X}_{IOE} \left(\mathbf{X}_{Ioi} - \frac{\sum_{j=1}^n \mathbf{X}_{Ioj} w_j(t) \hat{Y}_j^2(t)}{\sum_{j=1}^n w_j(t) \hat{Y}_j^2(t)} \right) \right] w_i(t) \hat{Y}_i^2(t) \boldsymbol{\beta}_0^T \mathbf{X}_{IOE} \mathbf{X}_{Ioi} dt \\ & \quad + n^{-1/2} \sum_{i=1}^n \int_0^{\tau} \left[\mathbf{X}_{IOE} \left(\mathbf{X}_{Ioi} - \frac{\sum_{j=1}^n \mathbf{X}_{Ioj} w_j(t) \hat{Y}_j^2(t)}{\sum_{j=1}^n w_j(t) \hat{Y}_j^2(t)} \right) \right] w_i(t) \hat{Y}_i(t) [\hat{R}_i(t) - R_i(t)] dM_i(t) \\ & \quad = n^{-1/2} \sum_{i=1}^n \int_0^{\tau} \left[\mathbf{X}_{IOE} \left(\mathbf{X}_{Ioi} - \frac{\sum_{j=1}^n \mathbf{X}_{Ioj} w_j(t) Y_j^{*2}(t)}{\sum_{j=1}^n w_j(t) Y_j^{*2}(t)} \right) \right] w_i(t) Y_i^*(t) dM_i^*(t) \\ & \quad + n^{-1/2} \sum_{i=1}^n \int_0^{\tau} \left[\mathbf{X}_{IOE} \left(\mathbf{X}_{Ioi} - \frac{\sum_{j=1}^n \mathbf{X}_{Ioj} w_j(t) Y_j^{*2}(t)}{\sum_{j=1}^n w_j(t) Y_j^{*2}(t)} \right) \right] w_i(t) Y_i^{*2}(t) \boldsymbol{\beta}_0^T \mathbf{X}_{IOE} \mathbf{X}_{Ioi} dt \\ & \quad + n^{-1/2} \sum_{i=1}^n \int_0^{\tau} \left[\mathbf{X}_{IOE} \left(\mathbf{X}_{Ioi} - \frac{\sum_{j=1}^n \mathbf{X}_{Ioj} w_j(t) Y_j^{*2}(t)}{\sum_{j=1}^n w_j(t) Y_j^{*2}(t)} \right) \right] w_i(t) Y_i^*(t) [\hat{R}_i(t) - R_i(t)] dM_i(t) + o_p(1) \\ & \quad = S_{21n} + S_{22n} + S_{23n}. \end{aligned}$$

For the first term, it is in the form of martingale integration, and we have

$$S_{21n} = n^{-1/2} \sum_{i=1}^n \Phi_{1i}(\tau) + o_p(1)$$

and

$$\text{Var}(S_{21n}) = n^{-1} \sum_{i=1}^n \int_0^{\tau} \left[\mathbf{X}_{IOE} \left(\mathbf{X}_{Ioi} - \frac{\sum_{j=1}^n \mathbf{X}_{Ioj} w_j(t) Y_j^{*2}(t)}{\sum_{j=1}^n w_j(t) Y_j^{*2}(t)} \right) \right]^{\otimes 2} w_i(t) Y_i^*(t) dN_i^*(t) + o_p(1)$$

converge to Ψ_{τ} with probability 1.

For the second term, we have

$$\begin{aligned}
S_{22n} &= n^{-1/2} \sum_{i=1}^n \int_0^\tau \left[\mathbf{X}_{IOE} \left(\mathbf{X}_{Ioi} - \frac{\sum_{j=1}^n \mathbf{X}_{Ioj} w_j(t) Y_j^{*2}(t)}{\sum_{j=1}^n w_j(t) Y_j^{*2}(t)} \right) \right] w_i(t) Y_i^{*2}(t) \beta_0^T \mathbf{X}_{IOE} \mathbf{X}_{Ioi} dt \\
&= n^{-1/2} \sum_{i=1}^n \int_0^\tau \left[\mathbf{X}_{IOE} \left(\mathbf{X}_{Ioi} - \frac{\sum_{j=1}^n \mathbf{X}_{Ioj} w_j(t) Y_j^{*2}(t)}{\sum_{j=1}^n w_j(t) Y_j^{*2}(t)} \right) \right] w_i(t) Y_i^{*2}(t) \mathbf{X}_{Ioi}^T \mathbf{X}_{IOE}^T \beta_0 dt \\
&= n^{-1/2} \sum_{i=1}^n \Phi_{2i}(\tau) + o_p(1).
\end{aligned}$$

Notice $\mathbf{X}_{IOE}^T \beta_0 = \beta_{0e} [\mathbf{X}_{Io}^T \mathbf{X}_{Io}]^{-1} \mathbf{X}_{Io}^T \mathbf{X}_e$; we can approximate S_{22n} by

$$\begin{aligned}
n^{-1/2} \sum_{i=1}^n \int_0^\tau \beta_{0e} \left[\mathbf{X}_{IOE} \left(\mathbf{X}_{Ioi} - \frac{\sum_{j=1}^n \mathbf{X}_{Ioj} w_j(t) Y_j^{*2}(t)}{\sum_{j=1}^n w_j(t) Y_j^{*2}(t)} \right) \right] \mathbf{X}_{Ioi}^T [\mathbf{X}_{Io}^T \mathbf{X}_{Io}]^{-1} \mathbf{X}_{Io}^T \mathbf{X}_e w_i(t) Y_i^{*2}(t) dt \\
\text{Var}(S_{22n}) = \frac{\sigma^2 \beta_{0e}^2}{n} \sum_{i=1}^n \int_0^\tau \left[\mathbf{X}_{IOE} \left(\mathbf{X}_{Ioi} - \frac{\sum_{j=1}^n \mathbf{X}_{Ioj} w_j(t) Y_j^{*2}(t)}{\sum_{j=1}^n w_j(t) Y_j^{*2}(t)} \right) \right] \mathbf{X}_{Ioi}^T [\mathbf{X}_{Io}^T \mathbf{X}_{Io}]^{-1} \mathbf{X}_{Ioi} \\
\times \left[\mathbf{X}_{IOE} \left(\mathbf{X}_{Ioi} - \frac{\sum_{j=1}^n \mathbf{X}_{Ioj} w_j(t) Y_j^{*2}(t)}{\sum_{j=1}^n w_j(t) Y_j^{*2}(t)} \right) \right]^T w_i(t) Y_i^{*2}(t) dt + o_p(1)
\end{aligned}$$

converge to Σ_τ with probability 1. The covariance between S_{11n} and S_{22n} converges to 0 with probability 1 as in [13].

Now, we look at the last term S_{23n} . Under same argument as [20], the empirical process and Lengart's inequality [32] with there approximations provide us

$$\sqrt{n} S_{23n} = n^{-1/2} \sum_{i=1}^n \int_0^\tau \frac{q(u)}{\pi(u)} dM_i^c(u) + o_p(1) = n^{-1/2} \sum_{i=1}^n \Phi_{3i}(\tau),$$

where

$$\begin{aligned}
q(u) &= -\lim_{n \rightarrow \infty} n^{-1} \sum_{i=1}^n \int_0^\tau \left[\mathbf{X}_{IOE} \left(\mathbf{X}_{Ioi} - \frac{\sum_{j=1}^n \tilde{\mathbf{X}}_i^T w_i(t) Y_i^{*2}(t)}{\sum_{j=1}^n w_i(t) Y_i^{*2}(t)} \right) \right] w_i(t) Y_i^{*2}(t) dM_i(t) I(t \geq u \geq T_i), \\
\pi(u) &= \lim_{n \rightarrow \infty} n^{-1} \sum_{i=1}^n I(T_i \geq u).
\end{aligned}$$

So the third-term variance is 0 and thus is ignorable comparing with the first two terms. As weighted estimating equation approach, the third term is asymptotically uncorrelated with first two terms, and thus, we obtain the asymptotic variance of the $\hat{\beta}$ as

$$\Omega_\tau^{-1} (\Psi_\tau + \sum_\tau) \Omega_\tau^{-1} \text{ with influence function } \Phi_I = \Phi_{1I} + \Phi_{2I} + \Phi_{3I}$$

A.3. Proof of Theorem 3

We will first study the performance of

$$-\log(1 - \hat{F}_1(t | X_e = x_e, X_o = x_o)) = \hat{H}_0^*(t) + t \hat{\beta}^T [x_e, x_o]. \text{ We can write this as}$$

$$\begin{aligned}
& n^{1/2}(\hat{H}_0^*(t) + t\hat{\beta}^T[x_e, \mathbf{x}_o] - H_0^*(t) - t\beta_0^T[x_e, \mathbf{x}_o]) \\
&= n^{1/2} \left(\frac{\int_0^t \sum_{i=1}^n w_i(s) \hat{Y}_i(s) [d\hat{N}_i(s) - \hat{Y}_i(s) \hat{\beta}^T \mathbf{X}_{IOE} \mathbf{X}_{IOI} ds]}{\sum_{i=1}^n w_i(s) \hat{Y}_i^2(s)} - H_0^*(t) + t(\hat{\beta} - \beta_0)^T[x_e, \mathbf{x}_o] \right) \\
&= n^{1/2} \left(\frac{\int_0^t \sum_{i=1}^n w_i(s) Y_i^*(s) [dN_i^*(s) - Y_i^*(s) \hat{\beta}^T \mathbf{X}_{IOE} \mathbf{X}_{IOI} ds]}{\sum_{i=1}^n w_i(s) Y_i^{*2}(s)} - H_0^*(t) + t(\hat{\beta} - \beta_0)^T[x_e, \mathbf{x}_o] \right) + o_p(1).
\end{aligned}$$

The first term can be written as $n^{-1/2} \sum_{i=1}^n \zeta_{1i}$ with covariance between two time t and t' as

$$\int_0^{t \wedge t'} \frac{n^{-1} \sum_{i=1}^n w_i^2(s) Y_i^{*2}(s) dN_i^*(s)}{[n^{-1} \sum_{i=1}^n w_i(s) Y_i^{*2}(s)]^2}$$

converge to $g(t \wedge t')$ in probability uniformly.

The second term has the covariance between two time t and t' as

$$tt'(x_e, \mathbf{x}_o) \Omega_\tau^{-1} (\Psi_\tau + \sum_\tau) \Omega_\tau^{-1} (x_e, \mathbf{x}_o)^T.$$

The covariance between two time t and t' for the first term and the second term converge in probability to

$$(x_e, \mathbf{x}_o) \Omega_\tau^{-1} \Gamma(t) t'.$$

So the martingale central limit theory provides the asymptotic of $-\log(1 - \hat{F}_1(t|X_e = x_e, \mathbf{X}_o = \mathbf{x}_o))$. Using -method, we can obtain the results in Theorem 3.

Figure 1.

Predicted cumulative incidence function of relapse comparing instrumental variable (IV) fitting to regular regression analysis. CIF, cumulative incidence function [Colour figure can be viewed at wileyonlinelibrary.com].

Figure 2. Predicted cumulative incidence function (CIF) of non-relapse mortality (NRM) comparing instrumental variable (IV) fitting with regular regression analysis [Colour figure can be viewed at wileyonlinelibrary.com].

Table 1

Simulation results comparing IV and traditional regression methods in terms of bias, SE, CR of 95% nominal confidence interval under different confounding levels (none/weak/strong), and IV strength (none/weak/strong).

Confounding	IV	n	50% Censoring						30% Censoring					
			IV method			Regression method			IV method			Regression method		
			Bias	SE	CR (%)	Bias	SE	CR (%)	Bias	SE	CR (%)	Bias	SE	CR (%)
None	None	100	5.78	37.62	96	0.02	0.52	93	3.96	33.22	97	-0.01	0.41	94
None	None	400	5.62	47.21	97	-0.00	0.24	90	3.17	37.01	97	-0.01	0.21	92
None	None	1000	-1.75	32.13	97	-0.01	0.13	95	-4.51	25.77	96	-0.01	0.12	95
None	Weak	100	-0.08	1.64	96	-0.01	0.50	92	-0.14	1.37	97	-0.03	0.41	95
None	Weak	400	-0.02	0.63	98	0.01	0.24	94	0.02	0.54	98	-0.00	0.20	92
None	Weak	1000	0.07	0.44	93	-0.00	0.13	97	0.06	0.39	94	-0.01	0.12	94
None	Strong	100	-0.03	0.71	94	-0.02	0.44	94	-0.06	0.57	96	-0.04	0.36	95
None	Strong	400	-0.01	0.32	98	0.00	0.20	94	0.02	0.27	98	-0.00	0.17	95
None	Strong	1000	0.03	0.23	95	0.00	0.12	97	0.02	0.19	96	0.00	0.11	95
Weak	None	100	5.66	34.67	96	-0.22	0.55	92	3.75	32.58	97	-0.23	0.45	90
Weak	None	400	5.61	52.28	97	-0.20	0.28	84	3.59	33.77	98	-0.21	0.23	82
Weak	None	1000	-1.56	39.24	92	-0.21	0.14	73	-3.90	29.79	93	-0.21	0.13	64
Weak	Weak	100	-0.04	1.74	95	-0.22	0.53	91	-0.08	1.41	96	-0.23	0.44	89
Weak	Weak	400	-0.04	0.69	97	-0.18	0.27	83	0.02	0.58	98	-0.18	0.23	86
Weak	Weak	1000	0.06	0.50	93	-0.18	0.14	80	0.05	0.43	94	-0.18	0.13	69
Weak	Strong	100	-0.03	0.77	96	-0.18	0.46	91	-0.04	0.61	98	-0.18	0.39	90
Weak	Strong	400	-0.02	0.35	97	-0.15	0.23	88	0.01	0.29	97	-0.14	0.19	88
Weak	Strong	1000	0.02	0.25	93	-0.13	0.13	88	0.02	0.22	95	-0.13	0.12	81
Strong	None	100	3.49	30.60	95	-0.45	0.58	84	2.48	19.67	96	-0.45	0.48	82
Strong	None	400	4.01	55.30	97	-0.40	0.31	67	2.10	35.71	97	-0.41	0.26	57
Strong	None	1000	-2.21	41.40	91	-0.41	0.16	28	-4.35	30.16	94	-0.41	0.15	25
Strong	Weak	100	0.08	2.07	96	-0.41	0.57	87	0.02	1.71	96	-0.41	0.47	84
Strong	Weak	400	-0.02	0.74	97	-0.36	0.30	68	0.04	0.61	98	-0.36	0.24	64
Strong	Weak	1000	0.03	0.54	91	-0.37	0.16	37	0.05	0.47	93	-0.36	0.15	27
Strong	Strong	100	0.00	0.89	95	-0.32	0.52	84	-0.02	0.69	96	-0.32	0.42	81

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		50% Censoring						30% Censoring						
Confounder	IV	n	IV method			Regression method			IV method			Regression method		
			Bias	SE	CR (%)	Bias	SE	CR (%)	Bias	SE	CR (%)	Bias	SE	CR (%)
Strong	Strong	400	-0.00	0.38	96	-0.28	0.26	73	0.02	0.31	98	-0.27	0.22	70
Strong	Strong	1000	0.02	0.28	93	-0.27	0.15	50	0.03	0.23	94	-0.27	0.13	42

IV, instrumental variable; SE, standard error; CR, coverage rate.

Table II

Fitting results for CIBMTR study using traditional regression with “year of TX” (model: 1) and without ‘year of TX’ (model: 2) and using “year of TX” as an instrumental variable (model: 3).

Outcome	Model	Variable	Coef. est. (SE)	p-value
Relapse	1	Ritux: yes vs no	−0.0022 (0.0016)	0.1774
Relapse	1	Age (years): 55 vs <55	0.0033 (0.0015)	0.0320
Relapse	1	Disease status: other vs CR1/PIF	0.0065 (0.0015)	<0.0001
Relapse	1	Prior lines of therapy: >2 vs 2	0.0081 (0.0019)	<0.0001
Relapse	1	Years of TX: 2000–2003 vs 1996–1999	−0.0035 (0.0015)	0.0162
Relapse	2	Ritux: yes vs no	−0.0043 (0.0015)	0.0036
Relapse	2	Age (years): 55 vs <55	0.0033 (0.0016)	0.0346
Relapse	2	Disease status: other vs CR1/PIF	0.0067 (0.0015)	<0.0001
Relapse	2	Prior lines of therapy: >2 vs 2	0.0083 (0.0019)	<0.0001
Relapse	3	Ritux: yes vs no	−0.0104 (0.0031)	0.0007
Relapse	3	Age (years): 55 vs <55	0.0038 (0.0016)	0.0175
Relapse	3	Disease status: other vs CR1/PIF	0.0063 (0.0015)	<0.0001
Relapse	3	Prior lines of therapy: >2 vs 2	0.0088 (0.0019)	<0.0001
NRM	1	Ritux: yes vs no	−0.0006 (0.0007)	0.3595
NRM	1	Age (years): 55 vs <55	0.0015 (0.0006)	0.0133
NRM	1	Time from DX to TX: >1 vs 1 year	0.0009 (0.0006)	0.1163
NRM	1	Karnofsky score: 90 vs <90	−0.0013 (0.0006)	0.0302
NRM	1	Karnofsky score: unknown vs < 90	0.0004 (0.0017)	0.8103
NRM	1	Years of TX: 2000–2003 vs 1996–1999	−0.0019 (0.0006)	0.0012
NRM	2	Ritux: yes vs no	−0.0017 (0.0006)	0.0060
NRM	2	Age (years): 55 vs <55	0.0014 (0.0006)	0.0218
NRM	2	Time from DX to TX: >1 vs 1 year	0.0009 (0.0006)	0.1307
NRM	2	Karnofsky score: 90 vs <90	−0.0013 (0.0006)	0.0328
NRM	2	Karnofsky score: Unknown vs <90	−0.0006 (0.0016)	0.7263
NRM	3	Ritux: yes vs no	−0.0049 (0.0012)	<0.0001
NRM	3	Age (years): 55 vs <55	0.0018 (0.0006)	0.0040
NRM	3	Time from DX to TX: >1 vs 1 year	0.0008 (0.0006)	0.1390
NRM	3	Karnofsky score: 90 vs <90	−0.0014 (0.0006)	0.0273
NRM	3	Karnofsky score: unknown vs <90	0.0001 (0.0018)	0.9510

Adjusted covariates include age, disease status and number of lines of chemotherapy for relapse/progression and age, time from diagnosis to treatment (DX to TX), and Karnofsky Score for NRM.

CIBMTR, Center for International Blood and Marrow Transplant Research; SE, standard error; NRM, non-relapse mortality.