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Instrumental variable estimation of the causal hazard ratio

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Abstract

Cox's proportional hazards model is one of the most popular statistical models to evaluate associations of exposure with a censored failure time outcome. When confounding factors are not fully observed, the exposure hazard ratio estimated using a Cox model is subject to unmeasured confounding bias. To address this, we propose a novel approach for the identification and estimation of the causal hazard ratio in the presence of unmeasured confounding factors. Our approach is based on a binary instrumental variable, and an additional no-interaction assumption in a first-stage regression of the treatment on the IV and unmeasured confounders. We propose, to the best of our knowledge, the first consistent estimator of the (population) causal hazard ratio within an instrumental variable framework. A version of our estimator admits a closed-form representation. We derive the asymptotic distribution of our estimator and provide a consistent estimator for its asymptotic variance. Our approach is illustrated via simulation studies and a data application.

KEYWORDS

causal inference, Cox model, marginal structural model, survival analysis, unmeasured confounding

1 | INTRODUCTION

In observational studies with a possibly right-censored outcome, the Cox proportional hazards model is by far the dominant analysis tool to infer the association between a treatment and an outcome. The associational measure here is the hazard ratio, that is, the ratio of instantaneous incidence rates between treatment groups. It is well-known that in observational studies, the hazard ratio estimated with a Cox model may be subject to unmeasured confounding.

A classical approach to deal with unmeasured confounding uses an instrumental variable. Intuitively, conditional on baseline covariates, an instrumental variable is an exogenous variable that is associated with the outcome only through its association with the treatment. The instrumental variable approach has been well-developed for the analysis of continuous and binary outcomes (e.g., Angrist et al., 1996; Abadie, 2003; Hernán & Robins, 2006; Wright & Wright, 1928; Wooldridge, 2010; Wang & Tchetgen Tchetgen, 2018) but less so for a right-censored survival outcome, particularly within the dominant Cox regression framework. This is mainly because the commonly used two-stage methods for instrumental variable estimation fail to provide consistent estimates due to non-collapsibility of the hazard ratio.

In this paper, we fill this gap by proposing a consistent estimator of the population-average causal hazard ratio in the case of an endogenous treatment variable, which to the best of our knowledge, is the first in the literature. We make the proportional causal hazard ratio assumption, which results in the so-called marginal structural Cox

model (Hernán et al., 2000). The marginal structural Cox model parameter can be interpreted as the causal hazard ratio. To identify the causal hazard ratio with a binary endogenous treatment variable, in addition to a valid binary instrument, we require a no-interaction assumption that the instrument and unmeasured confounders do not interact on the additive scale for their effects on the exposure. Our identification result builds on that of Wang and Tchetgen Tchetgen (2018), who establish identifiability of the average treatment effect on the additive scale under a similar assumption. Our assumption allows the outcome model to be completely unrestricted other than the marginal structural Cox model assumption, thus in sharp contrast to various treatment effect homogeneity assumptions previously used in the literature to identify population-average treatment effects with an instrument (e.g., Aronow & Carnegie, 2013; Hernán & Robins, 2006). Our identification formula readily leads to an estimating equation for the causal hazard ratio. To ease computation, we also develop a closed-form representation of the causal hazard ratio under our identification assumption. Although this might not directly improve the efficiency of the resulting estimator, it is particularly appealing computationally as without a closed-form representation, in practice it can be difficult to find a solution to an estimating equation. Even if one finds one solution, it can be difficult to check the uniqueness of such a solution. Our results may also be extended in a number of important directions. For example, it can be used to identify the cumulative baseline hazard function, the causal hazard ratio conditional on baseline covariates, and the cause-specific causal hazard ratio in a competing risk setting.

Our target of inference is different from the targets of most previous developments for instrumental variable estimation in a survival context, which are often motivated by randomized trials with non-compliance. The treatment effects considered by these proposals are defined within the so-called complier stratum, consisting of individuals who would comply with the assigned treatment under both active treatment and control. Such estimands include the complier hazard difference (Baker, 1998), the complier hazard ratio (Cuzick et al., 2007; Loeys & Goetghebeur, 2003), the complier quantile causal effect (Frandsen, 2015; Yu et al., 2015), the complier survival probabilities (Nie et al., 2011; Yu et al., 2015), and the complier average causal effect (Abadie, 2003; Cheng et al., 2009; Yu et al., 2015). However, in practice, the complier causal effects are often only of secondary interest as they concern a highly selective unknown subset of the population (Robins & Greenland, 1996). Furthermore, its definition depends on the particular instrument that is available (Wooldridge, 2010). This could potentially be a serious limitation outside of the non-compliance setting, especially when there is no natural choice of the instrument such as a randomized treatment assignment.

Our work instead contributes to the literature on instrumental variable estimation of population-average treatment effects in a survival context. Prior to our work, Robins and Tsiatis (1991) parameterized the treatment effect under a structural accelerated failure time model, Li et al. (2015), Tchetgen Tchetgen et al. (2015), and Martinussen et al. (2017) considered estimating the conditional hazard difference under a structural cumulative survival model, Martinussen et al. (2019), Sørensen et al. (2019), and Martínez-Camblor et al. (2019) considered estimating the causal hazard ratio among the treated, while Choi and O'Malley (2017) considered estimating the average treatment effect on the survival time. None of these methods, however, were designed to estimate the population-average causal hazard ratio, which is a natural target of inference given the popularity of the Cox model in practice. Although MacKenzie et al. (2014) had also considered instrumental variable estimation of the population-average causal hazard ratio, their estimating equation is only approximately unbiased under certain conditions. Furthermore, their approach relies on an instrument valid for estimating the effects of all the covariates and is limited to a somewhat artificial causal model (Tchetgen Tchetgen et al., 2015).

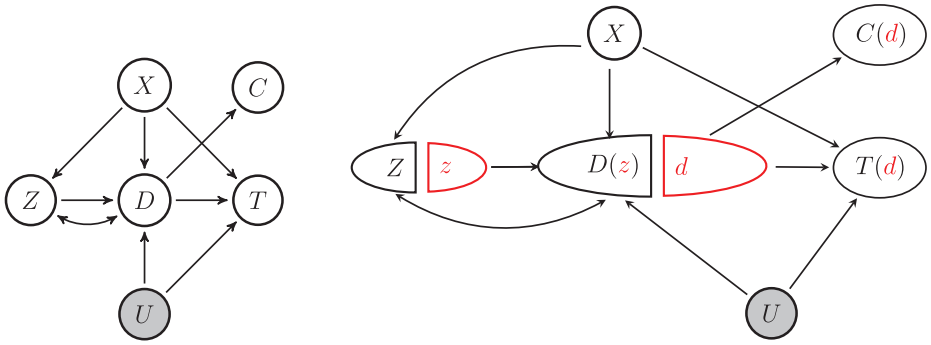
2 | BACKGROUND

2.1 | Framework and notation

Consider an observational study where the interest lies in estimating the effect of a binary treatment D on a possibly censored continuous survival outcome T. The effect of interest is subject to confounding by (a subset of) observed variables X as well as unobserved variables U. Let C denote the censoring time and Δ be the event indicator: $\Delta = I(T \leq C)$. The observed time $Y = \min(T, C)$. Let Z denote a binary instrumental variable with a 0–1 coding scheme. Using the framework of the potential outcome, let $D(z)$ be the potential exposure if the instrument had taken value z to be well-defined (the Stable Unit Treatment Value Assumption, Rubin, 1980). Similarly, we assume $T(d)$ and $C(d)$, the potential survival and censoring time if a unit were exposed to d to be well-defined. The potential survival function is defined as $S_d^T(t) = P(T(d) \geq t)$, and the potential hazard function is defined as $\lambda_d^T(t) = -[S_d^T(t)]'/S_d^T(t)$. Let $Y(d) = \min\{T(d), C(d)\}$. We may then similarly define $S_d^Y(y)$ and $\lambda_d^Y(y)$.

We assume the marginal structural Cox model:

$$\lambda_d^T(t) = \lambda_0^T(t)e^{\psi d}. \quad (1)$$



(A) A directed acyclic graph with a bi-directed arrow.

(B) A single world intervention graph with a bi-directed arrow.

FIGURE 1 Causal graphs representing the instrumental variable model defined by Assumptions 1–4. The bi-directed arrow between Z and D indicates potential unmeasured common causes of Z and D. Variables X, Z, D are observed; T is possibly right censored; U is unobserved. The left panel gives a causal directed acyclic graph (Pearl, 2009) with a bi-directed arrow, and the right panel gives a single-world intervention graph (Richardson & Robins, 2013) with a bi-directed arrow. This figure appears in color in the electronic version of this article, and any mention of color refers to that version.

We are interested in estimating ψ, the log of the causal hazard ratio.

We make the following assumptions commonly invoked in an instrumental variable analysis.

Assumption 1 (Independence). $Z \perp\!\!\!\perp U \mid X$.

Assumption 2 (Instrumental relevance). $Z \not\perp\!\!\!\perp D \mid X = x$, for all x in the support of X.

Assumption 3 (Sufficiency of U). $T(d), C(d) \perp\!\!\!\perp (D, Z) \mid (X, U)$.

Assumption 4 (Independent censoring). $C(d) \perp\!\!\!\perp T(d), d = 0, 1$.

We note that under the consistency assumption, Assumption 3 implies the exclusion restriction assumption $Z \perp\!\!\!\perp (T, C) \mid D, U, X$. Figure 1 gives a simple illustration of the conditional instrumental variable model. Under the consistency assumption, Assumptions 1–4 can be read off from the single-world intervention graph (Richardson & Robins, 2013) in Figure 1b via d-separation (Pearl, 2009). As pointed out by a reviewer, the causal graphs in Figure 1 need not be faithful; in particular, none of the links $X \to Z, X \to D$, or $X \to T$ is necessary. See Figure S1 in the Supporting information for an alternative causal graphical model that satisfies Assumptions 1–4.

One can see from the bi-directed arrows in Figure 1 that we allow for latent common causes of Z and D, so that the instrument Z and exposure D can be associated because Z has a causal effect on D, or because they share a common cause, or both. This is important as in observational study settings, it may not be realistic to assume that one has measured all common causes of Z and D.

To focus on the main challenges introduced by unmeasured confounding, we have assumed independent censoring as in Assumption 4. It can be extended to allow for censoring dependent on observed covariates X, that is,

$$C(d) \perp\!\!\!\perp T(d) \mid X, d = 0, 1. \tag{2}$$

See Proposition 2 for details.

Even with a valid instrument, in general, population-level causal effects are not identifiable from observed data. We now review some existing methods for identifying the average treatment effect in the literature.

2.2 | Instrumental variable methods

With a continuous outcome Y, a classical method to estimate the population average treatment is based on the following system of linear structural equation models:

$$D = \alpha_0 + \alpha_1 Z + \alpha_2 X + \alpha_3 U + \epsilon_D; \tag{3a}$$

$$Y = \beta_0 + \beta_1 D + \beta_2 X + \beta_3 U + \epsilon_Y. \tag{3b}$$

The two-stage least-squares (TSLS) method then proceeds as follows: one first regresses the treatment D on the instrument Z and covariates X to obtain $\widehat{D}$, and then regresses Y on $\widehat{D}$ and X to get the treatment effect estimate $\widehat{\beta}_1$. To illustrate the idea behind the TSLS, consider the simple case without X and ϵ_D. Without loss of generality, assume $E(U) = 0$ so that $\widehat{D}$ is approximately

$\alpha_0 + \alpha_1 Z$. In this case, Equations (3a) and (3b) imply that $Y = \beta_0 + \beta_1 \widehat{D} + (\alpha_3\beta_1 + \beta_3)U + \epsilon_Y$. Since $Z \perp\!\!\!\perp (U, \epsilon_Y)$, we have $\widehat{D} \perp\!\!\!\perp (U, \epsilon_Y)$ and $E[Y \mid \widehat{D}] = \beta_0 + \beta_1 \widehat{D}$. Hence, regressing Y on $\widehat{D}$ yields a consistent estimate for β_1.

The TSLS method, however, cannot be directly extended to obtain a consistent estimate for the causal hazard ratio. To see this, again consider the simple case without X and ϵ_D. Instead of Equation (3b), one may assume a structural Cox model:

$$\log \lambda(y \mid D, U, Z) = \log \lambda_0(y) + \gamma_1 D + \gamma_2 U. \tag{4}$$

Although under Equation (3a), we have $\log \lambda(y \mid \widehat{D}, U) = \log \lambda_0(y) + \gamma_1 \widehat{D} + (\alpha_3\gamma_1 + \gamma_2)U$, due to non-collapsibility of hazard ratio, in general $\log \lambda(y \mid \widehat{D}) \neq \log \lambda_0(y) + \gamma_1 \widehat{D}$. In this case, a two-stage predictor substitution (TSPS) method that fits a Cox model of Y on $\widehat{D}$ yields a biased estimate of γ_1 unless under degenerate circumstances such as $\gamma_1 = 0$ or $\alpha_3\gamma_1 + \gamma_2 = 0$. We refer interested readers to Wan et al. (2018, Section 4.3) for a detailed discussion of the bias from the TSPS method in the general case.

Remark 1. We further note that in the simple case without X and ϵ_D, γ_1 in Equation (4) denotes the log of the causal hazard ratio conditional on D, U, Z. Due to non-collapsibility of the hazard ratio, it is generally different from the log of the marginal causal hazard ratio, ψ.

In the linear case, the structural equation models (3a) and (3b) imply the following no-interaction assumptions:

$$E[D \mid Z = 1, X, U] - E[D \mid Z = 0, X, U] \perp\!\!\!\perp U, \tag{5a}$$

$$E[Y \mid D = 1, X, U] - E[Y \mid D = 0, X, U] \perp\!\!\!\perp U. \tag{5b}$$

Wang and Tchetgen Tchetgen (2018) showed that with a binary treatment D, if either Equation (5a) or (5b) holds, the average treatment effect β_1 can be identified and satisfies

$$\beta_1 = E\left\{ \frac{2Z - 1}{f(Z \mid X)\delta^D(X)} Y \right\}, \tag{6}$$

where $\delta^D(X) = E[D \mid Z = 1, X] - E[D \mid Z = 0, X]$ and $f(Z \mid X)$ denotes the conditional density of Z given X. We shall now build on Wang and Tchetgen Tchetgen (2018)'s work to identify the causal hazard ratio.

3 | IDENTIFICATION AND ESTIMATION OF THE CAUSAL HAZARD RATIO

3.1 | Identification of the causal hazard ratio

We now consider the identification problem of the log causal hazard ratio ψ. The results of Wang and Tchetgen Tchetgen (2018) imply that the average causal effect is identifiable without imposing assumptions on the outcome model, thus circumventing the difficulty introduced by non-collapsibility of the hazard ratio. Motivated by this, we shall pursue identification of the log causal hazard ratio ψ under assumption (5a) on the treatment generating model, which we formally state below.

Assumption 5. For U that satisfies Assumptions 1 and 3, there is no additive $U - Z$ interaction in $E[D \mid Z, X, U]$:

$$E[D \mid Z = 1, X, U] - E[D \mid Z = 0, X, U] = E[D \mid Z = 1, X] - E[D \mid Z = 0, X]. \tag{7}$$

When the instrument Z is randomized, Equation (7) is equivalent to $E[D(1) - D(0) \mid X, U] = E[D(1) - D(0) \mid X]$. Let $(D(1), D(0))$ be the compliance type (Wang and Tchetgen Tchetgen, 2018, Table 1). Then, Assumption 5 holds as long as there are no unmeasured confounders that also predict compliance type. The latter condition is closely related to the principal stratum homogeneity assumption that the causal effect is equal across principal strata (e.g., Aronow & Carnegie, 2013), which holds if the compliance type itself is not an (unmeasured) confounder. Note that due to non-collapsibility of the hazard ratio, even under the principal stratum homogeneity assumption, the complier hazard ratio is generally not equal to the marginal hazard ratio. So methods that identify complier hazard ratio may not directly be used to identify the marginal causal hazard ratio.

Remark 2. In general, there may be more than one set of unmeasured covariates U that satisfy Assumptions 1 and 3. We say that Assumption 5 holds if at least one of these sets of covariates U also satisfies Equation (7).

To identify the log hazard ratio ψ under Assumption 5, recall that the partial score equation in a regular Cox model (Cox, 1972) takes the following form:

$$H(\tau) = \mathbb{P}_n \int \left[W - \frac{\mathbb{P}_n\{W e^{\tau W} I(Y \geq y)\}}{\mathbb{P}_n\{e^{\tau W} I(Y \geq y)\}} \right] dN(y), \tag{8}$$

where $N(y) = I(Y \le y, \Delta = 1)$ is the counting process of observed failure events, $\mathbb{P}_n$ denotes empirical average, and W denotes the covariates in a regular Cox model.

Motivated by Equation (6), we consider a weighted version of Equation (8) by applying some weight function $\omega(Z,X,D)$ to the at risk process $I(Y \ge y)$ for each time point y. This results in the following estimating equation:

$$H(\psi) = \mathbb{P}_n \int dN(y)\omega(Z,X,D) \left[D - \frac{\mathbb{P}_n\{De^{\psi D} I(Y \ge y)\omega(Z,X,D)\}}{\mathbb{P}_n\{e^{\psi D} I(Y \ge y)\omega(Z,X,D)\}} \right]. \quad (9)$$

A natural choice for the weight function would be to use $\omega_0(Z,X) = (2Z-1)/\{f(Z|X)\delta^D(X)\}$, as in Equation (6). However, it will make Equation (9) ill-defined under large samples since $E\{e^{\psi D} I(Y \ge y)\omega_0(Z,X)\} = 0$ under the null that $\psi = 0$. To solve this problem, we add a stabilization term $h(D)$ to the weight function to ensure that Equation (9) is well-defined under large samples. Theorem 1 shows that the log causal hazard ratio ψ can indeed be uniquely identified via the population version of the estimating equation (9).

Theorem 1. *Under the marginal structural Cox model (1) and Assumptions 1–5, the causal hazard ratio is identifiable and is the unique solution to* $E\{H(\psi)\} = 0$, *where* $H(\psi)$ *is defined in (9),* $\omega(Z,X,D) = h(D)(2Z-1)/\{f(Z|X)\delta^D(X)\}$ *and* $h(D)$ *is any function of* D *such that* $h(1)h(0) < 0$.

Our weighted analyses here and in Equation (6) are similar in spirit to inverse probability weighting techniques commonly used in survival analysis to account for censoring (Robins & Rotnitzky, 1992), observed confounding (Hernán et al., 2000) and to detect early differences in survival times (weighted log-rank test, e.g., Fleming & Harrington, 2011).

Identification formula (9) directly leads to a weighting estimator for ψ. Suppose $f(Z \mid X;\eta)$ and $\delta^D(X;\beta)$ are finite-dimensional models on $f(Z \mid X)$ and $\delta^D(X)$, respectively. The parameter η can be estimated using the maximum likelihood estimator $\widehat{\eta}$. The conditional risk difference model $\delta^D(X;\beta)$, however, does not give rise to a likelihood by itself, so estimation of β relies on additional nuisance models. Choosing an appropriate nuisance model for estimating $\delta^D(X;\beta)$ is non-trivial, as a naive nuisance model on $p_0^D(X) = P(D = 1 \mid Z = 0, X)$ is not desirable: given models on $p_0^D(X)$ and $\delta^D(X)$, there is no guarantee that $p_1^D(X) = P(D = 1 \mid Z = 1, X) = p_0^D(X) + \delta^D(X)$ lies in the unit interval [0,1]. Instead, Richardson et al. (2017) developed a nuisance model $OP^D(X;\zeta)$, where $OP^D(X) = p_1^D(X)p_0^D(X)/\{(1-p_1^D(X))(1-p_0^D(X))\}$. It can be shown that with this parameterization, $p_1^D(X;\beta,\zeta)$ is guaranteed to lie in the unit interval, so that the maximum likelihood estimator (MLE) $(\widehat{\beta},\widehat{\zeta})$ may be obtained by unconstrained maximization. Alternatively, one may model $P(D = 1 \mid Z, X)$ directly using say, a logistic regression and then obtain a plug-in estimate for $\delta^D(X)$.

Remark 3. Although it seems more straightforward to use logistic regression models on $P(D = 1 \mid Z, X)$ to estimate $\delta^D(X)$, later in the simulations, we simulate data by specifying models on $\delta^D(X,U)$ and $OP^D(X,U)$ as it is easier to impose Assumption 5 this way. In particular, we simply let $\delta^D(X,U) = \delta^D(X)$ while $P(D = 1 \mid Z, X, U)$ still depends on U via $OP^D(X,U)$. If instead, one simulates data by specifying logistic models on $P(D = 1 \mid Z, X, U)$ directly, then to impose Assumption 5, one would typically need to assume that $P(D = 1 \mid Z = z, X, U)$ is independent of U, in which case U is not a confounder.

Equation (9) motivates an inverse probability weighting estimator, defined as a solution to the following equation:

$$\sum_{i=1}^{n} \Delta_i \widehat{\omega}(Z_i,X_i,D_i) \left[D_i - \frac{\sum_{j=1}^{n} \{D_j e^{\psi D_j} I(Y_j \ge Y_i)\widehat{\omega}(Z_j,X_j,D_j)\}}{\sum_{j=1}^{n} \{e^{\psi D_j} I(Y_j \ge Y_i)\widehat{\omega}(Z_j,X_j,D_j)\}} \right] = 0, \quad (10)$$

where $\widehat{\omega}(Z_i,X_i,D_i) = h(D_i)(2Z_i-1)/\{f(Z_i|X_i;\widehat{\eta})\delta^D(X_i;\widehat{\beta})\}$. Under suitable regularity conditions including correct specification of the models $f(Z \mid X;\eta), \delta^D(X;\beta), OP(X;\zeta)$, one can show that the solution to Equation (10) is asymptotically linear using standard empirical process theory. In practice, however, it may be computationally cumbersome to solve Equation (10). We address this problem in the next subsection by proposing an alternative estimator that is available in the closed form.

3.2 | A closed-form representation of the causal hazard ratio

To simplify Equation (9), a natural idea is to search for $h(D)$ such that

$$E\{De^{\psi D} I(Y \ge y)\omega(Z,X,D)\} = E\{\widetilde{g}(D) I(Y \ge y)\omega_0(Z,X)\} = 0, \quad (11)$$

where $\widetilde{g}(D) = h(D)De^{\psi D}$. If we can find such a $h(D)$, then Equation (9) becomes

$$H(\psi) = \int dN(y)\omega_0(Z,X)\widetilde{g}(D)e^{-\psi D}, \quad (12)$$

and $E\{H(\psi)\} = 0$ has a closed-form representation:

$$\exp(\psi) = \frac{E\int dN(y)(-D)\omega_0(Z,X)\widetilde{g}(1)}{E\int dN(y)(1-D)\omega_0(Z,X)\widetilde{g}(0)}. \quad (13)$$

Note, however, that it is not possible to identify $\exp(\psi)$ from Equation (13). This is because by construction, $\widetilde{g}(0) = 0$, so that the right-hand side of Equation (13) is not well-defined.

To solve this problem, instead of looking for $h(D)$, we shall directly look for a measurable function $g(D)$ so that $g(1)g(0) \neq 0$ and Equation (11) holds replacing $\widetilde{g}(D)$ with $g(D)$. In other words, we look for $g(D)$ that is orthogonal to $I(Y \geq y)\omega_0(Z,X)$ in the space $L_2(Z,X,Y,D)$. In general, all such functions may be represented as $\{m(D)E\{I(Y \geq y)\omega_0(Z,X)\} - E\{m(D)I(Y \geq y)\omega_0(Z,X)\} : m(D) \text{ is measurable}\}$. Theorem 2 shows that as long as $m(1) \neq m(0)$ so that $g(1)g(0) \neq 0$, Equation (13) holds replacing $\widetilde{g}(D)$ with $g(D)$.

Theorem 2. *Under the marginal structural Cox model (1) and Assumptions 1–5, we have*

$$\exp(\psi) = \frac{E\int dN(y)(-D)\omega_0(Z,X)\{m(1)\gamma_1(y) - \gamma_2^m(y)\}}{E\int dN(y)(1-D)\omega_0(Z,X)\{m(0)\gamma_1(y) - \gamma_2^m(y)\}}, \quad (14)$$

where $\gamma_1(y) = E\{I(Y \geq y)\omega_0(Z,X)\}, \gamma_2^m(y) = E\{m(D)I(Y$ *breakgey*$)\omega_0(Z,X)\}$ *and* $m(1) \neq m(0)$.

Theorem 2 can be extended in several directions. First, it can be extended to identify the cumulative baseline hazard function.

Proposition 1. *Under the marginal structural Cox model (1) and Assumptions 1–5, we have*

$$\Lambda_0(t) = \int_0^t \frac{E\{\omega_0(Z,X)dN(y)\}}{E\{\omega_0(Z,X)e^{\psi D}I(Y \geq y)\}}. \quad (15)$$

Identification formula (15) directly leads to a weighted version of the Breslow estimator (Breslow, 1972).

Second, it can be extended to allow for ignorable censoring.

Proposition 2. *Under the marginal structural Cox model (1), Assumptions 1–3,5 and condition (2), we have*

$$\exp(\psi) = \frac{E\int dN(y)(-D)\widetilde{\omega}(Z,X,D,y)\{m(1)\widetilde{\gamma}_1(y) - \widetilde{\gamma}_2^m(y)\}}{E\int dN(y)(1-D)\widetilde{\omega}(Z,X,D,y)\{m(0)\widetilde{\gamma}_1(y) - \widetilde{\gamma}_2^m(y)\}}, \quad (16)$$

where $\widetilde{\omega}(Z,X,D,y) = \omega_0(Z,X)\left(\frac{D}{P(C(1) \geq y \mid X)} + \frac{(1-D)}{P(C(0) \geq y \mid X)}\right)$, $\widetilde{\gamma}_1(y) = E\{I(Y \geq y)\widetilde{\omega}(Z,X,D,y)\}$ *and* $\widetilde{\gamma}_2^m(y) = E\{m(D)I(Y \geq y)\widetilde{\omega}(Z,X,D,y)\}$. *If we additionally assume that* $D \perp\!\!\!\perp C(d) \mid X$, *then* $P(C(d) \geq y \mid X) = P(C \geq y \mid X, D = d)$.

Third, it can be extended to identify parameters in the conditional structural Cox model:

$$\lambda_d^T(t \mid X) = \lambda_0^T(t \mid X)e^{\psi d}. \quad (17)$$

Proposition 3. *Under the conditional structural Cox model (17), Assumptions 1–3,5 and condition (2),*

$$\exp(\psi) = \frac{E\int dN(y)(-D)\overline{\omega}(Z,X)\{m(1)\overline{\gamma}_1(y,X) - \overline{\gamma}_2^m(y,X)\}}{E\int dN(y)(1-D)\overline{\omega}(Z,X)\{m(0)\overline{\gamma}_1(y,X) - \overline{\gamma}_2^m(y,X)\}}, \quad (18)$$

where $\overline{\omega}(Z,X) = \overline{h}(X)(2Z-1)/\{f(Z \mid X)\}, \overline{\gamma}_1(y,X) = E\{I(Y \geq y)\overline{\omega}(Z,X) \mid X\}, \overline{\gamma}_2^m(y,X) = E\{m(D)I(Y \geq y)\overline{\omega}(Z,X) \mid X\}$, $m(1) \neq m(0)$ *and* $\overline{h}(X)$ *is any non-zero measurable function of* X.

Fourth, it can be extended to accommodate the case of competing risks. Let $(T(d), \epsilon(d))$ denote the potential time to one of the competing events, where $\epsilon(d) \in \{1, \ldots, K\}$ keeps track of which of the K competing events would happen under exposure d. Let $S_d^{T,k}(t) = P(T(d) \geq t, \epsilon(d) = k)$ and $\lambda_d^{T,k}(t) = \lim_{dt \to 0} P(t \leq T(d) < t + dt, \epsilon(d) = k \mid T(d) \geq t)/dt$ be the corresponding cause-specific survival and hazard functions, and $N^k(t) = I(Y \leq t, \Delta = 1, \epsilon = k)$ be the cause-specific counting process. The cause-specific marginal structural Cox model is:

$$\lambda_d^{T,k}(t) = \lambda_0^{T,k}(t)e^{\psi_k d}, k = 1, \ldots, K. \quad (19)$$

Proposition 4. *Suppose that the cause-specific marginal structural Cox model (19), Assumptions 1, 2, 5 and the following conditions hold:*

*A3** $(T(d), \epsilon(d), C(d)) \perp\!\!\!\perp (D, Z) \mid (X, U)$;
*A4** $C(d) \perp\!\!\!\perp (T(d), \epsilon(d)), d = 0, 1$.

Then, we have

$$\exp(\psi_k) = \frac{E\int dN^k(y)(-D)\omega_0(Z,X)\{m(1)\gamma_1(y) - \gamma_2^m(y)\}}{E\int dN^k(y)(1-D)\omega_0(Z,X)\{m(0)\gamma_1(y) - \gamma_2^m(y)\}}, \quad (20)$$

where $m(D), \gamma_1(y), \gamma_2^m(y)$ *satisfy the same conditions as in Theorem 2.*

Fifth, in the case of rare events, the no U–Z interaction Assumption 5 may be replaced by a no U–d interaction on the hazard ratio scale:

$$\lambda_d^T(t \mid X, U) = \lambda_0^T(t \mid X, U)e^{\beta(X)d}. \quad (21)$$

Proposition 5. *Suppose that condition (21), Assumptions 1–3, and the following conditions hold:*

*A4** (Independent censoring)* $T(d) \perp\!\!\!\perp C(d) \mid X, U$, *and* $Z \perp\!\!\!\perp C \mid X, U$;

A5 (Rare event)* $S_d^T(y \mid X, U) = P(T(d) \geq y \mid X, U) \approx 1$ *for all* y *in a finite follow-up period.*

Then, we have

$$\exp(\beta(X)) \approx \frac{\int E[dN(y)(-D)\dfrac{2Z-1}{f(Z \mid X)} \mid X]}{\int E[dN(y)(1-D)\dfrac{2Z-1}{f(Z \mid X)} \mid X]}. \quad (22)$$

In particular, if $\beta(X)$ *is a constant function of* X, *then the conditional Cox model (21) approximates the marginal Cox model (1) with* $\psi = \beta(X)$. *In this case,*

$$\exp(\psi) \approx \frac{\int E[dN(y)(-D)\dfrac{2Z-1}{f(Z \mid X)} h_1(X)]}{\int E[dN(y)(1-D)\dfrac{2Z-1}{f(Z \mid X)} h_1(X)]} \quad (23)$$

for any non-zero measurable function $h_1(X)$.

Proposition 5 may also be extended to accommodate competing risks.

Corollary 1. *If one assumes that*

$$\lambda_d^{T,k}(t \mid X, U) = \lambda_0^{T,k}(t \mid X, U) e^{\beta_k(X)d}, k = 1, \ldots, K. \quad (24)$$

*Then under Assumptions 1–3, A4**, A5*, and the assumption that* $Z \perp\!\!\!\perp Y(d), \epsilon(k) \mid X, U$, *we have*

$$\exp(\beta_k(X)) \approx \frac{\int E[dN^k(y)(-D)\dfrac{2Z-1}{f(Z \mid X)} \mid X]}{\int E[dN^k(y)(1-D)\dfrac{2Z-1}{f(Z \mid X)} \mid X]}. \quad (25)$$

If $\beta_k(X), k = 1, \ldots, K$ *are constant functions of* X, *then the conditional cause-specific Cox models (24) approximate the marginal cause-specific Cox model (19) with* $\psi_k = \beta_k(X)$ *and*

$$\exp(\psi_k) \approx \frac{\int E[dN^k(y)(-D)\dfrac{2Z-1}{f(Z \mid X)} h_1^k(X)]}{\int E[dN^k(y)(1-D)\dfrac{2Z-1}{f(Z \mid X)} h_1^k(X)]} \quad (26)$$

for any non-zero measurable functions $h_1^k(X), k = 1, \ldots, K$.

3.3 | Estimation

In Theorem 2, a natural choice for $m(D)$ is $m(D) = D$. Under the modeling assumptions described in Section 3.1, Equation (14) gives rise to the following estimator:

$$\widehat{\psi} = \log \frac{\sum_{i=1}^n \Delta_i D_i \widehat{\omega}_0(Z_i, X_i)\left\{\widehat{\gamma}_{1,i} - \widehat{\gamma}_{2,i}^{m_0}\right\}}{\sum_{i=1}^n \Delta_i (1-D_i)\widehat{\omega}_0(Z_i, X_i)\widehat{\gamma}_{2,i}^{m_0}}, \quad (27)$$

where $\widehat{\omega}_0(Z_i, X_i) = (2Z_i - 1)/\{f(Z_i|X_i; \widehat{\eta})\delta^D(X_i; \widehat{\beta})\}$, $\widehat{\gamma}_{1,i} = \widehat{\gamma}_1(Y_i)$, $\widehat{\gamma}_{2,i}^{m_0} = \widehat{\gamma}_2^{m_0}(Y_i)$ with

$$\begin{aligned}\widehat{\gamma}_1(y) &= n^{-1}\sum_{j=1}^n I(Y_j \geq y)\widehat{\omega}_0(Z_j, X_j), \widehat{\gamma}_2^{m_0}(y) \\ &= n^{-1}\sum_{j=1}^n D_j I(Y_j \geq y)\widehat{\omega}_0(Z_j, X_j). \end{aligned} \quad (28)$$

We now discuss large sample properties for our proposed estimator (27). Note that $\widehat{\psi}$ solves the equation $\mathbb{P}_n\{H(\psi, \widehat{\theta})\} = 0$, where $\theta = (\beta, \eta)$ and

$$\begin{aligned} H(\psi, \widehat{\theta}) = \int &\left[\{\widehat{\gamma}_1(y) - \widehat{\gamma}_2^{m_0}(y)\}D\right. \\ &\left.-(1-D)\widehat{\gamma}_2^{m_0}(y)\right] \widehat{\omega}_0(Z, X) e^{-\psi D} dN(y). \end{aligned} \quad (29)$$

It follows from Van der Vaart (2000, Lemma 5.10) that $\widehat{\psi}$ is a consistent estimator of ψ_0. We may further write $\mathbb{P}_n H(\psi_0, \theta_0) = \mathbb{P}_n H^c(\psi_0, \theta_0) + o_p(1/\sqrt{n})$, where

$$\begin{aligned} H^c(\psi_0, \theta_0) = \int &\left[\{\gamma_1(y) - \gamma_2^{m_0}(y)\}D\right. \\ &\left.-(1-D)\gamma_2^{m_0}(y)\right] \omega_0(Z, X) \left\{e^{-\psi D} dN(y)\right. \\ &\left.-R(y) d\Lambda_0(y)\right\} \end{aligned} \quad (30)$$

with $R(y) = I(Y \geq y)$ and $\Lambda_0(y) = \int_0^y \lambda_0(s)\, ds$. The $H_i^c(\psi_0, \theta_0)$'s are zero-mean terms that are independent and identically distributed. We hence have the following theorem.

Theorem 3. *Suppose that the marginal structural Cox model (1) and the nuisance models* $f(Z \mid X; \eta), \delta^D(X; \beta), OP(X; \zeta)$ *are correctly specified. Under Assumptions 1–5, we have that* ψ *is asymptotically linear with influence function given by* $IF_{\widehat{\psi}} = -E\{\partial H(\psi, \theta_0)/\partial\psi|_{\psi=\psi_0}\}^{-1}\widetilde{H}(\psi_0, \theta_0)$, *where* $\widetilde{H}(\psi_0, \theta_0) = H^c(\psi_0, \theta_0) + E\{\dfrac{\partial H(\psi_0, \theta)}{\partial\theta}|_{\theta=\theta_0}\} IF_{\widehat{\theta}}$ *with* $IF_{\widehat{\theta}}$ *being the influence function of* $\widehat{\theta}$.

A consistent estimator of $n\text{var}(\widehat{\psi})$ is $\mathbb{P}_n\{\widehat{IF}_{\widehat{\psi}}\}^2$, where $\widehat{IF}_{\widehat{\psi}}$ is obtained from $IF_{\widehat{\psi}}$ by replacing unknown quantities with their empirical counterparts.

Remark 4. When the sample size is small, it is possible that Equation (27) is undefined as the term inside the logarithm is non-positive.

4 | SIMULATION STUDIES

We now compare the finite sample performance of our proposed estimator $\widehat{\psi}$ to various other estimators proposed in the literature. In our simulations, the baseline covariates X include an intercept, a continuous variable X_2 generated from an exponential distribution with mean $1/\lambda_2$, and $X_3 = X_2 I(X_2 \geq 1) - (X_2 + 1)I(X_2 < 1)$. These choices and the generating models below ensure that $\delta^D(X)$ is bounded away from 0, so that the instrumental relevance assumption holds. The unmeasured confounder U is generated from an independent exponential distribution with mean $1/\lambda_1$. Conditional on X and U, the instrument Z and treatment D are generated from the following models: $P(Z = 1 \mid X) = \text{expit}(-1/\lambda_2 + X_2), \delta^D(X, U) = \tanh(\beta_0 + \beta_1 X_2 + \beta_2 X_3 + \beta_3 U)$, and $\log(OP^D(X, U)) = \zeta_0 + \zeta_1 U + \zeta_2 X_2$, where $\lambda_1 = \lambda_2 = 2, \zeta_0 = -2, \zeta_1 = \zeta_2 = 1$. We let $(\beta_0, \beta_1, \beta_2) = (0.5, 0.5, 0)$ or $(0, 0, 0.5)$. Moreover, the first set of parameter values is compatible with the commonly used monotonicity assumption that $D(1) \geq D(0)$ almost surely, as $\delta^D(X)$ is always positive. The censoring time C was generated from an exponential distribution with mean $1/\lambda$. As discussed in detail in Richardson et al. (2017), our specifications of $\delta^D(X)$ and $\log(OP^D(X))$ give rise to a unique model on $P(D = 1 \mid Z = z, X), z = 0, 1$. Visualizations of such a model can be found in Richardson et al. (2017, Supporting information, upper panels of Figure 1). To make the observed data models compatible with a marginal structural Cox model with parameter ψ, as explained in the Supporting information, we let the survival outcome T be the unique root of the following function (Tchetgen Tchetgen & Robins, 2012):

$$f(t) = \frac{1}{\lambda_1}(\lambda_1 - \kappa_1 t)\frac{1}{\lambda_2}(\lambda_2 - \kappa_2 t)\exp\left\{(\kappa_1 U + \kappa_2 X_2 - \lambda_0 e^{\psi D})t\right\} - 1 + A, \tag{31}$$

where $\psi = 0.5, \lambda_0 = 4, \kappa_1 = \kappa_2 = 1$ and A is uniformly distributed on the interval [0,1].

In addition to the proposed estimator (27), we also implement the following estimators: (i) Cox-crude: a crude Cox proportional model not adjusting for any covariates; (ii) Cox-adj: a Cox model adjusting for covariates (X_2, X_3); (iii) Cox-MSM: marginal structural Cox model adjusting for (X_2, X_3); (iv) MacKenzie: MacKenzie et al. (2014)'s method; (v) TSPS: a naive application of the two-stage least-square method, with a first-stage linear model and a second-stage Cox model; (vi) TSRI: a naive application of the two-stage residual inclusion method (Terza et al., 2008), with a first-stage linear model and a second-stage Cox model.

All simulation results are based on 1000 Monte-Carlo runs of $n = 1000$ units each. Table 1 summarizes the simulation results. When $\beta_3 = 0$ such that Assumption 5 holds, the biases from Cox regression estimates Cox-crude, Cox-adj and Cox-MSM are large, due to unmeasured confounding by U. MacKenzie et al. (2014)'s method, TSPS and TSRI are also biased, while the bias of the proposed estimator is small relative to its standard deviation; see also Table S1 in the Supporting information. Consistent with previous results in the literature (Wan et al., 2018), the bias of TSRI is in general smaller than that of the TSPS. Results in Table 2 show that Wald-type 95% confidence intervals constructed using the proposed variance estimator also achieve the nominal coverage rate in all the scenarios under which Assumption 5 holds, confirming our theoretical results. Given a fixed data-generating mechanism for the censoring time C, the censoring rate only increases with ψ slightly. When $\beta_3 = 0.5$ so that Assumption 5 fails to hold, MacKenzie et al. (2014)'s estimator produces an invalid estimate in one of the 1000 Monte Carlo runs; all the other estimators produce valid estimates in all Monte Carlo runs. The proposed estimator $\widehat{\psi}$ has a large bias only when the monotonicity condition fails and $\psi = 0.5$. The 95% confidence intervals, however, are only slightly conservative. For example, when $\psi = 0.5, \lambda = 4$ and monotonicity fails, although the bias of $\widehat{\psi}$ (4.8) is much larger than its standard error (1.0), it is much smaller compared to its standard deviation (31.6). As a rule of thumb, the performance of interval estimates begins to deteriorate when the bias is more than 40% of standard deviation (e.g., Kang & Schafer, 2007). So, it is not surprising to see that in this case, the coverage probability, 96.6%, is only slightly larger than the nominal level.

5 | APPLICATION TO THE HEALTH INSURANCE PLAN STUDY

In this section, we illustrate the proposed method by revisiting the Health Insurance Plan study, a randomized trial of mammography screening from 1963 to 1982. The goal was to determine whether screening reduced breast cancer mortality in women. Around 60,695 women aged between 40 and 60 were randomized into two groups. Half of them, in the study group, were assigned to receive two annual

TABLE 1 Censoring rate and bias times 100 (standard error times 100, in parenthesis) for various methods estimating the log causal hazard ratio ψ

	Censoring %	Bias×100 (SE ×100)						
A5 holds (β_3=0)		**Proposed**	**Cox − crude**	**Cox − adj**	**Cox − MSM**	**MacKenzie**	**TSPS**	**TSRI**
Monotonicity holds								
$\lambda = 0$	0	0.41(0.44)	5.4(0.22)	1.5(0.23)	2.5(0.27)	5.7(0.35)	−3.9(0.35)	0.26(0.35)
$\lambda = 1$	17.2%	0.47(0.48)	5.5(0.24)	1.5(0.25)	2.6(0.29)	5.9(0.38)	−2.4(0.39)	0.20(0.39)
$\lambda = 4$	44.9%	0.97(0.58)	5.7(0.29)	1.8(0.30)	2.6(0.34)	6.7(0.44)	0.19(0.47)	0.65(0.47)
Monotonicity fails								
$\lambda = 0$	0	−0.21(0.45)	3.1(0.21)	1.7(0.22)	−3.8(0.30)	−7.4(0.53)	−8.9(0.47)	−3.2(0.49)
$\lambda = 1$	17.0%	−0.38(0.49)	3.2(0.23)	1.7(0.23)	−4.0(0.32)	−7.5(0.58)	−7.4(0.53)	−2.9(0.54)
$\lambda = 4$	44.6%	−0.65(0.60)	2.9(0.28)	1.2(0.28)	−4.3(0.39)	−8.8(0.69)	−6.2(0.64)	−3.6(0.65)
A5 fails ($\beta_3 = 0.5$)								
Monotonicity holds								
$\lambda = 0$	0	−0.31(0.36)	5.1(0.22)	1.2(0.22)	2.1(0.30)	4.6(0.30)	−4.0(0.30)	0.00(0.29)
$\lambda = 1$	17.2%	−0.29(0.39)	5.2(0.24)	1.3(0.24)	2.2(0.32)	4.7(0.33)	−2.7(0.33)	0.02(0.33)
$\lambda = 4$	44.8%	0.06(0.47)	5.6(0.28)	1.6(0.29)	2.4(0.38)	5.6(0.38)	−0.22(0.40)	0.50(0.40)
Monotonicity fails								
$\lambda = 0$	0	2.5(0.72)	3.7(0.20)	2.1(0.21)	−3.3(0.30)	−10(0.97)	−8.1(0.87)	−3.7(0.89)
$\lambda = 1$	17.2%	2.5(0.80)	3.9(0.22)	2.2(0.22)	−3.4(0.32)	−11(1.1)	−7.0(0.97)	−3.7(0.99)
$\lambda = 4$	44.8%	2.6(0.97)	3.8(0.27)	2.0(0.27)	−3.4(0.40)	−14(1.3)	−7.2(1.2)	−5.1(1.2)

Note: The true value for ψ is 0.5. Here, "monotonicity holds" refer to the case where $\delta^D(X) > 0$ for all X. The sample size is 1000. Results are based on 1000 simulated datasets.

TABLE 2 Range of censoring rate, bias times 100 (standard error times 100, in parenthesis), and coverage rate for the proposed method estimating the log causal hazard ratio ψ

	Censoring rate	Bias×100 (SE ×100)		Coverage rate	
Assumption 5 holds		$\psi = 0$	$\psi = 0.5$	$\psi = 0$	$\psi = 0.5$
Monotonicity holds					
$\lambda = 0$	0	−0.43(0.41)	−0.26(0.43)	0.952	0.949
$\lambda = 1$	17.2%–20.0%	−0.53(0.46)	−0.24(0.47)	0.954	0.951
$\lambda = 4$	44.8%–50.0%	−0.28(0.58)	−0.01(0.57)	0.961	0.956
Monotonicity fails					
$\lambda = 0$	0	0.37(0.43)	0.41(0.44)	0.945	0.951
$\lambda = 1$	17.0%–20.0%	0.52(0.48)	0.56(0.48)	0.940	0.953
$\lambda = 4$	44.5%–50.0%	0.61(0.60)	0.73(0.59)	0.950	0.956
Assumption 5 fails		$\psi = 0$	$\psi = 0.5$	$\psi = 0$	$\psi = 0.5$
Monotonicity holds					
$\lambda = 0$	0	−0.19(0.34)	−0.69(0.35)	0.952	0.946
$\lambda = 1$	17.1%–20.0%	−0.27(0.37)	−0.69(0.38)	0.955	0.948
$\lambda = 4$	44.7%–50.0%	−0.14(0.47)	−0.61(0.46)	0.956	0.955
Monotonicity fails					
$\lambda = 0$	0	0.34(0.67)	3.2(0.70)	0.951	0.960
$\lambda = 1$	17.1%–20.0%	0.71(0.76)	3.8(0.79)	0.948	0.960
$\lambda = 4$	44.7%–50.0%	1.2(1.0)	4.8(1.0)	0.963	0.966

Note: The nominal coverage rate is 95%. Here, "monotonicity holds" refers to the case where $\delta^D(X) > 0$ for all X. The sample size is 1000. Results are based on 1000 simulated datasets.

breast examinations that include mammography, a breast exam, and an interview. The control group continued to receive their usual care. About 35% of women offered screening (9,984 out of 30,130) refused to participate, so there was a significant portion of non-compliers. Furthermore, study women with a higher risk for breast cancer tended to comply: the incidence rate among study group women who refused screening was 1.45 per 1,000, versus 1.87 per 1,000 among control group women. So, a direct comparison between the women who accepted screening, and women who did not receive screening, is subject to unmeasured confounding. The same data were used by Joffe (2001) to estimate the causal effect under an accelerated failure time model, and Martinussen et al. (2017) to estimate the conditional causal hazard difference. Instead, we shall use the proposed method to estimate the marginal causal hazard ratio due to mammography screening.

Following previous analyses by Joffe (2001) and Martinussen et al. (2017), we focus on the first 10 years of follow-up to reduce attenuation of the effects of the screening. We consider the randomization variable as our instrument Z, and the indicator of receiving screening as our exposure D. Our primary outcome of interest is breast cancer mortality. For verification purposes, we also consider a secondary outcome, death due to other causes, for which we expect the causal effect of breast cancer screening to be null. In the first 10 years of follow-up, there were 4,221 deaths but only 340 were deemed due to breast cancer. Note that the independence and instrumental relevance assumptions hold by design as the instrument is randomized and only subjects assigned to the treatment group may receive screening. The exclusion restriction is plausible because randomization to the study group is unlikely to affect mortality directly, had a study women chosen to refuse screening. We adjust for baseline covariate age, as a predictor of compliance behavior.

We then use the proposed methods in Section 3 to estimate the marginal causal hazard ratio. To accommodate the two competing outcomes we consider here, we shall apply the results in Proposition 4 (denoted as Proposed). In addition, since the outcomes are relatively rare, we also apply Corollary 1 (denoted as Proposed-rare-event). In doing so, we assume that cause-specific hazard ratios $\beta_k(X), k = 1, 2$ are constant functions of X, so that it targets the same parameters as Proposed. We also assume that $h_1^k(X) = 1, k = 1, 2$ in Corollary 1. For comparison purpose, we also implement the estimators Cox-crude, Cox-adj, Cox-MSM, MacKenzie, TSPS, and TSRI, in which except for Cox-crude and MacKenzie, we adjust for the baseline covariate age.

Table 3 summarizes the results. The crude and adjusted Cox regression model and the marginal structural Cox model all suggest that breast cancer screening is negatively associated with breast cancer mortality (hazard ratio: 0.77, 0.77, 0.79). Such associations, however, may be distorted by the fact that the screening group is at higher risk for breast cancer compared to the group that did not receive screening. Based on this reason, one would expect that the effect of breast cancer screening would be stronger than what these associations suggested. Indeed, our analysis based on the identification formula outlined in Proposition 4 suggests that breast cancer screening reduces the hazard of death due to breast cancer, with a hazard ratio of 0.67 (95% CI = [0.50,0.89]). Furthermore, as expected, breast cancer screening has little effect for deaths of reasons other than breast cancer, with a hazard ratio of 0.99 (95% CI = [0.90, 1.09]). Our proposed methods assuming rare events and no D–U interaction in the Causal Cox model, yield very similar results to that assuming no Z–U interaction in an additive model for the treatment.

Both MacKenzie and the two-stage methods TSLS and TSRI yield similar point estimates to our proposed estimator, with slightly larger variances. In this application, the random assignment to the study group is a valid instrumental variable even without conditioning on age, so the unconditional IV model assumed by MacKenzie is also valid. Moreover, the outcomes considered in this example are rare, in which case both MacKenzie and the two-stage methods are known to be approximately unbiased (MacKenzie et al., 2014; Tchetgen Tchetgen et al., 2015). These results confirm the findings from our primary analysis based on the identification formula outlined in Proposition 4.

6 | DISCUSSION

In this paper, we considered the identification and estimation of the marginal causal hazard ratio under the proportional hazards assumption. Our framework can also be extended in the following directions. First, in longitudinal studies, it is often the case that both the treatment and confounding variables are time dependent. It would be interesting to extend the proposed methods to estimate parameters in a marginal structural Cox model with time-varying treatments. This has been done for the effect of treatment among the treated under the Cox regression model (Martínez-Camblor et al., 2019) but not for the marginal causal hazard ratio which is defined under a marginal structural Cox model. Second, with an uncensored outcome, one can construct a locally efficient estimator for the population treatment effect of interest that is also multiply robust in the sense that such an estimator is consistent in the union of three different observed data models (Wang and Tchetgen Tchetgen, 2018). Deriving a locally semiparametric efficient estimator for the

TABLE 3 Point estimates (95% CI) for hazard ratio of breast cancer screening on death due to different reasons

Method	Death due to breast cancer	Death due to other causes
Cox-crude	0.77 (0.61,0.97)	1.40 (1.30, 1.50)
Cox-adj	0.77 (0.61,0.97)	1.37 (1.28, 1.47)
Cox-MSM	0.79 (0.62, 1.01)	0.66 (0.61, 0.71)
MacKenzie	0.66 (0.46, 0.94)	0.99 (0.90, 1.08)
TSPS	0.66 (0.48, 0.92)	0.99 (0.90, 1.09)
TSRI	0.67 (0.45, 0.99)	0.96 (0.86,1.07)
Proposed	0.67 (0.50,0.89)	0.99 (0.90, 1.09)
Proposed-rare-event	0.68 (0.51,0.90)	1.02 (0.91, 1.15)

causal hazard ratio under our identification assumptions is an important venue for future research. Third, so far we have restricted our analysis to a single binary instrument and a binary exposure. It has been shown that the framework in Wang and Tchetgen Tchetgen (2018) can be extended to allow for general instruments and exposure (Hartwig et al., 2020). We leave this as future work to extend the proposed method to the case of general instruments and exposure.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this paper are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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REFERENCES

Abadie, A. (2003) Semiparametric instrumental variable estimation of treatment response models. *Journal of Econometrics*, 113(2), 231–263.

Angrist, J.D., Imbens, G.W. & Rubin, D.B. (1996) Identification of causal effects using instrumental variables. *Journal of the American Statistical Association*, 91, 444–455.

Aronow, P.M. & Carnegie, A. (2013) Beyond LATE: estimation of the average treatment effect with an instrumental variable. *Political Analysis*, 21(4), 492–506.

Baker, S.G. (1998) Analysis of survival data from a randomized trial with all-or-none compliance: estimating the cost-effectiveness of a cancer screening program. *Journal of the American Statistical Association*, 93(443), 929–934.

Breslow, N.E. (1972) Contribution to discussion of paper by DR Cox. *Journal of the Royal Statistical Society: Series B*, 34, 216–217.

Cheng, J., Qin, J. & Zhang, B. (2009) Semiparametric estimation and inference for distributional and general treatment effects. *Journal of the Royal Statistical Society: Series B (Statistical Methodology)*, 71(4), 881–904.

Choi, J. & O'Malley, A.J. (2017) Estimating the causal effect of treatment in observational studies with survival time end points and unmeasured confounding. *Journal of the Royal Statistical Society: Series C (Applied Statistics)*, 66(1), 159–185.

Cox, D.R. (1972) Regression models and life-tables. *Journal of the Royal Statistical Society: Series B (Methodological)*, 34(2), 187–202.

Cuzick, J., Sasieni, P., Myles, J. & Tyrer, J. (2007) Estimating the effect of treatment in a proportional hazards model in the presence of non-compliance and contamination. *Journal of the Royal Statistical Society: Series B (Statistical Methodology)*, 69(4), 565–588.

Fleming, T.R. & Harrington, D.P. (2011) *Counting processes and survival analysis*. Vol. 169. John Wiley & Sons.

Frandsen, B.R. (2015) Treatment effects with censoring and endogeneity. *Journal of the American Statistical Association*, 110(512), 1745–1752.

Hartwig, F.P., Wang, L., Smith, G.D. & Davies, N. (2020) Average causal effect estimation via instrumental variables: the no simultaneous heterogeneity assumption. *arXiv:2010.10017*.

Hernán, M.Á., Brumback, B. & Robins, J.M. (2000) Marginal structural models to estimate the causal effect of zidovudine on the survival of HIV-positive men. *Epidemiology*, 11(5), 561–570.

Hernán, M.A. & Robins, J.M. (2006) Instruments for causal inference: An epidemiologist's dream? *Epidemiology*, 17(4), 360–372.

Joffe, M.M. (2001) Administrative and artificial censoring in censored regression models. *Statistics in Medicine*, 20(15), 2287–2304.

Kang, J.D. & Schafer, J.L. (2007) Demystifying double robustness: A comparison of alternative strategies for estimating a population mean from incomplete data. *Statistical Science*, 22(4), 523–539.

Li, J., Fine, J. & Brookhart, A. (2015) Instrumental variable additive hazards models. *Biometrics*, 71(1), 122–130.

Loeys, T. & Goetghebeur, E. (2003) A causal proportional hazards estimator for the effect of treatment actually received in a randomized trial with all-or-nothing compliance. *Biometrics*, 59(1), 100–105.

MacKenzie, T.A., Tosteson, T.D., Morden, N.E., Stukel, T.A. & O'Malley, A.J. (2014) Using instrumental variables to estimate a Cox's proportional hazards regression subject to additive confounding. *Health Services and Outcomes Research Methodology*, 14(1-2), 54–68.

Martínez-Camblor, P., Mackenzie, T., Staiger, D.O., Goodney, P.P. & O'Malley, A.J. (2019) Adjusting for bias introduced by instrumental variable estimation in the cox proportional hazards model. *Biostatistics*, 20(1), 80–96.

Martínez-Camblor, P., MacKenzie, T.A., Staiger, D.O., Goodney, P.P. & James O'Malley, A. (2019) An instrumental variable procedure for estimating Cox models with non-proportional hazards in the presence of unmeasured confounding. *Journal of the Royal Statistical Society: Series C (Applied Statistics)*, 68(4), 985–1005.

Martinussen, T., Nørbo Sørensen, D. & Vansteelandt, S. (2019) Instrumental variables estimation under a structural Cox model. *Biostatistics*, 20(1), 65–79.

Martinussen, T., Vansteelandt, S., Tchetgen Tchetgen, E.J. & Zucker, D.M. (2017) Instrumental variables estimation of exposure effects on a time-to-event endpoint using structural cumulative survival models. *Biometrics*, 73, 1140–1149.

Nie, H., Cheng, J. & Small, D.S. (2011) Inference for the effect of treatment on survival probability in randomized trials with noncompliance and administrative censoring. *Biometrics*, 67(4), 1397–1405.

Pearl, J. (2009) *Causality*. Cambridge, England: Cambridge University Press.

Richardson, T.S. & Robins, J.M. (2013) Single world intervention graphs (SWIGs): A unification of the counterfactual and graphical approaches to causality. *Center for the Statistics and the Social Sciences, University of Washington Series. Working Paper, 128*.

Richardson, T.S., Robins, J.M. & Wang, L. (2017) On modeling and estimation for the relative risk and risk difference. *Journal of the American Statistical Association*, 112(519), 1121–1130.

Robins, J.M. & Greenland, S. (1996) Identification of causal effects using instrumental variables: Comment. *Journal of the American Statistical Association*, 91(434), 456–458.

Robins, J.M. & Rotnitzky, A. (1992) Recovery of information and adjustment for dependent censoring using surrogate markers. In *AIDS Epidemiology* (pp. 297–331). Springer.

Robins, J.M. & Tsiatis, A.A. (1991) Correcting for non-compliance in randomized trials using rank preserving structural failure time models. *Communications in Statistics-Theory and Methods*, 20(8), 2609–2631.

Rubin, D.B. (1980) Comment. *Journal of the American Statistical Association*, 75(371), 591–593.

Sørensen, D.N., Martinussen, T. & Tchetgen Tchetgen, E. (2019) A causal proportional hazards estimator under homogeneous or heterogeneous selection in an IV setting. *Lifetime Data Analysis*, 25(4), 639–659.

Tchetgen Tchetgen, E.J. & Robins, J. (2012) On parametrization, robustness and sensitivity analysis in a marginal structural cox proportional hazards model for point exposure. *Statistics & Probability Letters*, 82(5), 907–915.

Tchetgen Tchetgen, E.J., Walter, S., Vansteelandt, S., Martinussen, T. & Glymour, M. (2015) Instrumental variable estimation in a survival context. *Epidemiology (Cambridge, Mass.)*, 26(3), 402–410.

Terza, J.V., Basu, A. & Rathouz, P.J. (2008) Two-stage residual inclusion estimation: addressing endogeneity in health econometric modeling. *Journal of Health Economics*, 27(3), 531–543.

Van der Vaart, A.W. (2000) *Asymptotic Statistics*, volume 3. Cambridge University Press.

Wan, F., Small, D. & Mitra, N. (2018) A general approach to evaluating the bias of 2-stage instrumental variable estimators. *Statistics in Medicine*, 37(12), 1997–2015.

Wang, L. & Tchetgen Tchetgen, E. (2018) Bounded, efficient and multiply robust estimation of average treatment effects using instrumental variables. *Journal of the Royal Statistical Society: Series B (Statistical Methodology)*, 80, 531–550.

Wooldridge, J.M. (2010) *Econometric analysis of cross section and panel data*. Cambridge, MA: MIT press.

Wright, P.G. & Wright, S. (1928) *The tariff on animal and vegetable oils*. New York: The Macmillan Co.

Yu, W., Chen, K., Sobel, M.E. & Ying, Z. (2015) Semiparametric transformation models for causal inference in time-to-event studies with all-or-nothing compliance. *Journal of the Royal Statistical Society: Series B (Statistical Methodology)*, 77(2), 397–415.

SUPPORTING INFORMATION

Tables, Figures, Proofs of theorems, propositions and claims referenced in Sections 2, 3 and 4 are available with this paper at the Biometrics website on Wiley Online Library. Code for implementing the proposed method in equation (27) is available both on Wiley Online Library and on Harvard Dataverse: https://doi.org/10.7910/DVN/FL4KFL.

Figure S1: An alternative causal diagram compatible with the instrumental variable assumptions 1–4. Variables X, Z, D are observed, where $X = (X1, X2)$; T is possibly right censored.

Table S1: Censoring rate and relative bias times 100 (standard error times 100, in parenthesis) for various methods estimating the log causal hazard ratio ψ.

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