Defining and Estimating Subgroup Mediation Effects with Semi-Competing Risks Data

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Abstract

In many medical studies, an ultimate failure event such as death is likely to be affected by the occurrence and timing of other intermediate clinical events. Both event times are subject to censoring by loss-to-follow-up but the nonterminal event may further be censored by the occurrence of the primary outcome, but not vice versa. To study the effect of an intervention on both events, the intermediate event may be viewed as a mediator, but conventional definition of direct and indirect effects is not applicable due to semi-competing risks data structure. We define three principal strata based on whether the potential intermediate event occurs before the potential failure event, which allow proper definition of direct and indirect effects in one stratum whereas total effects are defined for all strata. We discuss the identification conditions for stratum-specific effects, and proposed a semiparametric estimator based on a multivariate logistic stratum membership model and within-stratum proportional hazards models for the event times. By treating the unobserved stratum membership as a latent variable, we propose an EM algorithm for computation. We study the asymptotic properties of the estimators by the modern empirical process theory and examine the performance of the estimators in numerical studies.

Keywords: Illness-death model; Missing data; Principal stratification; Proportional hazards model; Survival analysis.
1. Introduction

Evaluating the causal effects of an intervention on a clinical outcome is a common theme in many medical studies. After an overall relationship between the intervention and outcome is established, it is often of further interest to understand the biological or mechanistic pathways that contribute to the causal treatment effect. Causal mediation analysis is often utilized to disentangle the total treatment effect by decomposing it into the indirect effect, i.e., the effect exerted by intermediate variables (mediators), and the direct effect, i.e., the effect involving pathways independent of the hypothesized mediators. A number of methods were proposed for causal mediation analysis with survival outcomes, for a single mediator measured at study entry (Lange and Hansen 2011; VanderWeele 2011; Tchetgen Tchetgen 2011; Lange et al. 2012) and for longitudinal mediators (Lin et al. 2017; Zheng and van der Laan 2017; Didelez 2019; Vansteelandt et al. 2019; Aalen et al. 2020).

In many biomedical studies, intermediate, non-terminal landmark events are recorded in addition to the primary failure event because they are important to evaluate prognosis. Due to the ordering of the two events, the non-terminal event is subject to censoring by the occurrence of the terminal event, but not vice versa, such that semi-competing risks data are observed (Fine et al. 2001). In this paper, we consider a setting where a non-terminal event may serve as a mediator for individuals to whom the event would occur before the terminal event. An example is a multi-center trial of allogeneic bone marrow transplants in patients with acute leukemia (Copelan et al. 1991; Klein and Moeschberger 2006), where the primary interest is on the effect of different treatment regimen (methotrexate + cyclosporine vs methylprednisolone + cyclosporine) on the survival time. The event time of an intermediate endpoint, chronic graft-versus-host disease (GVHD), is a major side effect of the transplant that can be lethal. However, some patients died without experiencing GVHD, such that GVHD event time is subject to censoring by the death time.
Causal mediation analysis with semi-competing risks data is particularly challenging. First, the mediator is only well-defined for those who would have the non-terminal event developed before the occurrence of the primary event. Therefore, the conventional definition of natural indirect and direct effects based on replacing the counterfactual of mediator under one treatment by that under the other can hardly apply to the entire population. This challenge is similar to that of the ‘truncation-by-death’ problem (Zhang and Rubin 2003, Comment et al. 2019), where the primary outcome is only available if the terminal event does not occur. However, there is a substantial difference in that the primary outcome of interest is the terminal event in our setting. Moreover, the semi-competing risks data structure, that is, the primary event may censor the intermediate event but not vice versa, posts additional challenges in the identifiability of parameters. Upon finishing this paper, we became aware of the newly accepted paper by Huang (2020) which considered this problem by a counting process framework. The problem formulation, estimand and assumptions are all very different from our work. For instance, we do not make sequential ignorability assumptions on surviving subpopulations at arbitrary post-treatment time, because those evolving subpopulations are generally healthier than the baseline study population before the treatment is assigned.

In this paper, we consider a novel principal stratification approach to define causal mediation effects in the subgroup where the intermediate event happens when given either treatment, i.e., those susceptible to the intermediate event under both treatments. The notations and settings are given in Sections 2.1 and 2.2. We discuss the identification conditions needed for estimating the stratum-specific natural indirect and direct effects in Section 2.3, and proposed a semiparametric estimator based on a multivariate logistic stratum membership model and within-stratum proportional hazards models for the event times in Section 2.4. By treating the unobserved stratum membership as a latent variable, we propose an EM algorithm for computation of the nonparametric maximum likelihood
estimator in Section 2.5. We also study the asymptotic properties of the estimators using the modern empirical process theory in Section 2.6 and examine the performance of the estimators in simulation studies Section 3. An analysis of data from a clinical trial is given in Section 4, and concluding remarks are included in Section 5. Proofs and detailed derivations are given in the Appendix.

2. Methods

2.1. Notations for Observed Data

Let $A$ be a binary treatment, $T$ be the time to a primary event of interest and $M$ be the time to an intermediate, non-terminal event. The intermediate event time $M$ may be censored by the occurrence of the primary event, but not vice versa, such that we observe semi-competing risks data. For example, $A$ is a treatment for prolonging survival time, $T$ is the time to death, and $M$ is the time to cancer progression. The occurrence of death may censor the cancer progression onset, but not vice versa.

Let $X$ be a collection of baseline covariates that may be associated with either or both events. Let $C$ denote a censoring time for the primary event, for example, end of follow-up time. Then, we observe $Y \equiv \min(T, C)$ and $\Delta^T = I(T \leq C)$ for the primary event, and $Z \equiv \min(M, Y)$ and $\Delta^M = I(M \leq Y)$ for the intermediate event. The observations are versions of the counterfactual variables that we define as follows.

2.2. Counterfactuals and Causal Estimands

To define causal mediation effects of interest, we adopt the potential outcomes framework. In conventional causal mediation analysis based on counterfactuals, $M(a)$ denotes the counterfactual nonterminal event time when the treatment is set to $a$ and $T(a, m)$ denotes the counterfactual terminal event time when the treatment is set to $a$ and the nonterminal event time (mediator) is set to $m$. A comparison of $T(a, M(a))$ with $T(a, M(a^*))$ would
define a measure of the natural indirect effect of changing the mediator from $M(a)$ to $M(a^*)$ and a comparison of $T(a, M(a^*))$ with $T(a^*, M(a^*))$ would define a measure of the natural direct effect of changing the treatment from $a$ to $a^*$. Both natural indirect and direct effects involve the term $T(a, M(a^*))$, i.e., the counterfactual outcome for the terminal event time when the treatment is set to $a$ and the nonterminal event time is set to $M(a^*)$, the counterfactual nonterminal event time when the treatment is set to $a^*$.

However, these conventional definitions are inadequate for semi-competing risk settings and needs to be modified for the following reasons. The potential non-terminal event may or may not occur before the potential primary event time under different treatment assignments. When the potential primary event happens before the potential intermediate event, the value of the mediator is not well-defined (and is often set to $\infty$ by convention) and in such a case the potential primary event time shall not be dependent on an arbitrary $m$ greater than the potential primary event time. Due to these considerations, we examine causal effects based on our proposed principal stratification approach, extended from Frangakis and Rubin (2002). Intuitively, we stratify the study population into latent classes identified by $U$ with 3 categories based on whether they are susceptible to the non-terminal event under different treatment assignments. For an individual with $U = 1$, we assume the residual counterfactual event time $T(a, m) - m$ is non-negative with probability 1 for $m \in \mathcal{M}$, where $\mathcal{M}$ is the support of $M(a)$. This does not only imply susceptibility under either treatment, but also implies $T(a, M(a^*)) > M(a^*)$ for $a \neq a^*$. For $U = 2$, we assume $M(1) = \infty$ with probability 1, and $T(1, m)$ is only defined for $m = \infty$, while $(T(0, m), M(0))$ is defined for $m \in \mathcal{M}$ such that $T(0, m) - m$ is non-negative with probability 1. That is, the treatment “prevents” the subject with $U = 2$ from having the intermediate event. For individuals with $U = 3$, we assume $M(0) = M(1) = \infty$ with probability 1 and $T(a, m)$ is defined for $a \in \{0, 1\}$ with $m = \infty$. That is, they are always “non-susceptible” to the non-terminal event. Here, we assume that the fourth stratum with
the nonterminal event only present in the treated does not exist. This restriction is along the same line as the “no defier” assumption commonly adopted in the instrumental variables methods, suggesting that the treatment effect is “monotone” and no reversed effect for the subjects (Angrist et al. 1996).

Remark 1. The defined strata (and associated stratum-specific effects) are substantially different from the survivors’ principal stratum (and the survivor average causal effect (SACE)) that is commonly defined in “truncation by death” literature (Zhang and Rubin 2003; Comment et al. 2019). In particular, the survivors’ principal stratum is defined by \( \{T(0) \geq t, T(1) \geq t\} \) for some fixed time \( t \) in Comment et al. (2019), whereas our definition does not depend on any arbitrary post-treatment time \( t \).

Remark 2. Lin et al. (2017) explained the difficulties in defining natural mediation effects in survival context with longitudinal mediators. They defined interventional effects in a discrete-time setting, where the mediators and past survival status are subject to a hypothetical intervention. They mentioned that principal stratification as an alternative framework to avoid such hypothetical intervention, but did not explore further. We consider a different setting that shares some of the difficulties, but also with unique data structure so that principal strata can be defined.

Using our modified definition, the convention \( T(a) = T(a, M(a)) \) still holds for all individuals, while \( T(a, M(a^*)) \), \( a \neq a^* \), is only well-defined for \( U = 1 \). Therefore, the stratum-specific indirect and direct effects can only be defined for subjects with \( U = 1 \), while total effects are still well-defined for \( U = 2 \) and \( U = 3 \). In light of these observations, for stratum with \( U = 1 \), we define the stratum-specific natural indirect and direct effects as

\[
NIE_1(t; x) = \Pr\{T(1, M(1)) \geq t|X = x, U = 1\} - \Pr\{T(1, M(0)) \geq t|X = x, U = 1\}
\]

(1)
and

\[ NDE_1(t; x) = \Pr\{T(1, M(0)) \geq t|X = x, U = 1\} - \Pr\{T(0, M(0)) \geq t|X = x, U = 1\}. \]

(2)

In stratum with \( U = 2 \), \( T(1, M(0)) \) is not well-defined because \( T(1, m) \) is only defined for \( m = \infty \) and \( M(0) < \infty \) with probability 1. However, \( T(a) = T(a, M(a)) \) is still well-defined and the stratum-specific total effect is

\[ TE_2(t; x) = \Pr\{T(1) \geq t|X = x, U = 2\} - \Pr\{T(0) \geq t|X = x, U = 2\}. \]

In stratum with \( U = 3 \), \( M(0) = M(1) = \infty \) and \( T(1, M(0)) = T(1, M(1)) \) so there is no indirect effect. The stratum-specific total effect can still be defined as

\[ TE_3(t; x) = \Pr\{T(1) \geq t|X = x, U = 3\} - \Pr\{T(0) \geq t|X = x, U = 3\}. \]

Remark 3. In principle, a mediator shall satisfy temporal precedence, that it shall occur before the primary event. Therefore, one can view that the mediator is technically absent in \( U = 3 \), and an attempt to define mediation effects would be futile. In \( U = 2 \), the presence of the mediator before the primary event only happens in one treatment level with certainty. As a result, one cannot fix the mediator level at a different treatment level, and mediation effects cannot be defined. Note that in \( U = 2 \), \( TE_2 \) can be interpreted as the treatment effect in survival among individuals whose mediating events are prevented by the treatment.

2.3. Identification

To identify the stratum-specific natural indirect and direct effects and stratum-specific total effects, we impose the following assumptions.

**Assumption 1** (Consistency). If \( A = a \), then \( M = M(a) \) and \( T = T(a) \) with probability 1; if \( A = a \), and \( M = m \), then \( T = T(a, m) \) with probability 1.
Assumption 2 (Sequential Ignorability within Stratum). For \( a = 0, 1, a^* = 0, 1, m \in (0, \tau], \) and \( u = 1, 2, 3, \)
\[
\{T(a,m), M(a^*)\} \perp A|X, U = u
\]
and
\[
T(a,m) \perp M|A = a^*, X, U = u.
\]

Assumptions \([1]\) is a standard assumption for causal inference with no unmeasured confounding. Assumption \([2]\) is a standard assumption for mediation analysis in \( U = 1. \) For \( U = 2, 3, \) Assumption \([2]\) reduces to the standard assumption of conditional exchangeability within stratum. Based on Assumptions \([1] - [2]\) we are able to connect the stratum-specific natural indirect and direct effects and stratum-specific total effects with the distribution of the observed data given stratum membership as follows.

**Theorem 1.** Under Assumptions \([1] - [2]\) for stratum with \( U = 1, \) the stratum-specific natural indirect effect \( NIE_1(t; x) \) is equal to
\[
\int_0^t \{1 - \Pr(T < t|M = m, X = x, A = 1, U = 1)\} \\
\times \{dF_{M|X=x,A=1,U=1}(m) - dF_{M|X=x,A=0,U=1}(m)\} \\
+ \Pr(M \leq t|X = x, A = 0, U = 1) - \Pr(M \leq t|X = x, A = 1, U = 1),
\]
and the stratum-specific natural direct effect \( NDE_1(t; x) \) is equal to
\[
\int_0^t \{\Pr(T < t|M = m, X = x, A = 0, U = 1) \\
- \Pr(T < t|M = m, X = x, A = 1, U = 1)\} dF_{M|X=x,A=0,U=1}(m).
\]

Under Assumptions \([1]\) and \([2]\) for stratum with \( U = 2, \) the stratum-specific total effect \( TE_2(t; x) \) is equal to
\[
\Pr(T \geq t|A = 1, X = x, U = 2) - \Pr(T \geq t|A = 0, X = x, U = 2);
\]

7
and for stratum with $U = 3$, the stratum-specific total effect $TE_3(t; x)$ is equal to

$$\Pr(T \geq t | A = 1, X = x, U = 3) - \Pr(T \geq t | A = 0, X = x, U = 3).$$

The proof of Theorem 1 is given in Appendix A.1. Since $U$ is unobserved, we cannot use Theorem 1 directly to identify those stratum-specific effects from observed data. To do so, one would further assume

**Assumption 3** (Stratum Membership Independent of Treatment). With probability one, $U$ is conditional independent of $A$ given $X$.

**Assumption 4** (Restriction on Stratum-Specific Distributions). With probability one,

$$\Pr(M(0) = m | X = x, U = 2) = g_1 \{ \Pr(M(0) = m | X = x, U = 1); x \},$$
$$\Pr(T(0) \geq t | M(0) = m, X = x, U = 2) = g_2 \{ \Pr(T(0) \geq t | M(0) = m, X = x, U = 1); x \},$$
$$\Pr(T(1) \geq t | X = x, U = 2) = g_3 \{ \Pr(T(1) \geq t | X = x, U = 3); x \},$$

for some known functions $g_k(\cdot; x)$ ($k = 1, 2, 3$).

**Assumption 5** (Non-Informative Censoring and Sufficient Follow-up). $(M, T, U)$ is conditionally independent of $C$ given $A$ and $X$, and the upper bound of the support of $T$ is no larger than that of $C$.

Assumption 3 requires that the stratum membership is not affected by the treatment assignment $A$ given covariates $X$. Assumption 4 requires some knowledge on the relationships of stratum-specific event time distributions. The first part of Assumption 5 is a standard assumption for non-informative censoring time. The second part of Assumption 5 is an extension of the independent censoring and sufficient follow-up assumption in Maller and Zhou (1992) for nonparametric estimation of cured proportion in censored data. The assumption on the upper bounds of the supports ensures sufficient observation of the tail.
behaviour of the event times for identification of stratum membership. By further assuming Assumptions 3 - 5 we obtain the identification results in Theorem 2, whose proof is given in Appendix A.2.

**Theorem 2.** Under Assumptions 1 - 5, the stratum-specific effects can be identified, with identification formulas given in (A.2) - (A.5).

Theorem 2 gives the identification result based on nonparametric models for $U$ and for $(M, T)$ given $U$ with minimum assumptions. In particular, Assumption 4 requires some modeling assumptions to be made. In practice, we may consider additional model assumptions for $U$ and $(M, T)$ to gain power in understanding the causal effects. In the next section, we extend the multistate modeling idea in the literature of semi-competing risks data to form such a model.

### 2.4. Modeling assumptions

One way to model semi-competing risks data is to use a multistate framework (Xu et al. 2010). In multistate analysis of semi-competing risks data, usually three states (states 1 - 3) are involved, corresponding to healthy (state 1), illness (state 2), and death (state 3) in an illness-death model. All subjects starts at state 1. A subject enters state 2 if he/she develops the intermediate event, while he/she enters state 3 if he/she develops the primary event. In traditional illness-death model for semi-competing risks data, three processes moving from one state to another are modeled: (1) healthy to illness (state 1 to 2), (2) illness to death (state 2 to 3), and (3) healthy to death (state 1 to 3).

Here, we extend the idea and model the processes moving from one state to another in different strata defined in Section 2.2. For subjects with $U = 1$ and subjects with $U = 2$ receiving $A = 0$, the processes of healthy to illness and illness to death are involved and we model the time to the nonterminal event $M$ and the residual time $R = T - M$. We assume that $M$ and $R$ are conditionally independent given $A, X$, and $U$. This serves two
purposes: to obtain a tractable EM algorithm in Appendix B, and to avoid the problem of induced informative censoring caused by residual dependence between $M$ and $R$ (Wang and Wells 1998; Lin et al. 1999). For subjects with $U = 2$ receiving $A = 1$ and subjects with $U = 3$, the process of healthy to death is involved. This proposed model is related to but different from the illness-death model, in that the transition structure depends on the principal strata in our proposed model.

Suppose that for a subject with $U = 1$, the nonterminal event time follows a proportional hazards model with hazard function given by

$$\lambda_M^{(1)}(t|A = a, \mathbf{X} = \mathbf{x}) = \lambda_1(t) \exp (\beta_{M1} a + \gamma_T^{M1} \mathbf{x}),$$

and the gap time between the occurrences of nonterminal and terminal events $R$ follows a proportional hazards model with hazard function given by

$$\lambda_R^{(1)}(r|A = a, \mathbf{X} = \mathbf{x}) = \lambda_2(r) \exp (\beta_{R1} a + \gamma_T^{R1} \mathbf{x}).$$

Suppose that for subject with $U = 2$ and unexposed to treatment ($A = 0$), the nonterminal event time follows a proportional hazards model with hazard function given by

$$\lambda_M^{(2)}(t|A = 0, \mathbf{X} = \mathbf{x}) = \lambda_1(t) \exp (\beta_{M2} + \gamma_T^{M2} \mathbf{x}),$$

and the gap time between the occurrences of nonterminal and terminal events follows another proportional hazards model with hazard function given by

$$\lambda_R^{(2)}(r|A = 0, \mathbf{X} = \mathbf{x}) = \lambda_2(r) \exp (\beta_{R2} + \gamma_T^{R2} \mathbf{x}).$$

Here, subjects with $U = 1$ and subjects with $U = 2$ unexposed to treatment share the same baseline hazard functions, although the hazard ratios for covariates may be different. The parameters $\beta_{M1}$ and $\beta_{R1}$ are the log hazard ratios of treatment on the nonterminal event time and gap time, respectively, for subjects with $U = 1$; the parameters $\beta_{M2}$ and $\beta_{R2}$ are
the log hazard ratios on the nonterminal event time and gap time, respectively, comparing subjects with \( U = 1 \) and \( U = 2 \) who both unexposed to treatment with baseline covariates value \( X = 0 \).

For subject with \( U = 2 \) and exposed with treatment \((A = 1)\), we assume that the terminal event time follows a proportional hazards model with hazard function given by
\[
\lambda_T^2(t|A = 1, X = x) = \lambda_3(t) \exp \left( \beta_{R2} + \gamma_{R2}^T x \right).
\]

For subject with \( U = 3 \), we suppose that the terminal event time follows a proportional hazards model with hazard function given by
\[
\lambda_T^3(t|A = a, X = x) = \lambda_3(t) \exp \left( \beta_{R3} a + \gamma_{R3}^T x \right).
\]

Note that the terminal event times for subject with \( U = 3 \) and subject with \( U = 2 \) exposed to treatment share the same baseline hazard function. The parameter \( \beta_{R3} \) is the log hazard ratio of treatment on the terminal event time for subjects with \( U = 3 \), while \( \beta_{R2} \) is the log hazard ratio of the terminal event time comparing subjects with \( U = 3 \) and \( A = 0 \) with subjects with \( U = 2 \) and \( A = 1 \), with the same covariates value \( X = 0 \).

The natural indirect and direct effects in stratum with \( U = 1 \) can be presented as
\[
NIE_1(t|X = x) = \int_0^t \exp \left\{ -\Lambda_2(t - m) e^{\beta_{R1} + \gamma_{R1}^T x} \right\} \lambda_1(m) e^{\gamma_{M1}^T x}
\times \left[ e^{\beta_{M1}} \exp \left\{ -\Lambda_1(m) e^{\gamma_{M1}^T x} \right\} - \exp \left\{ -\Lambda_1(m) e^{\gamma_{M1}^T x} \right\} \right] dm
+ \exp \left\{ -\Lambda_1(t) e^{\beta_{M1} + \gamma_{M1}^T x} \right\} - \exp \left\{ -\Lambda_1(t) e^{\gamma_{M1}^T x} \right\}
\]
and
\[
NDE_1(t|X = x) = \int_0^t \left[ \exp \left\{ -\Lambda_2(t - m) e^{\beta_{R1} + \gamma_{R1}^T x} \right\} - \exp \left\{ -\Lambda_2(t - m) e^{\gamma_{R1}^T x} \right\} \right]
\times \lambda_1(m) e^{\gamma_{M1}^T x} \exp \left\{ -\Lambda_1(m) e^{\gamma_{M1}^T x} \right\} dm,
\]
where \( \Lambda_1(t) = \int_0^t \lambda_1(s) \, ds \) and \( \Lambda_2(t) = \int_0^t \lambda_2(s) \, ds \). The total effects in strata with \( U = 2 \) and \( U = 3 \) are given by

\[
TE_2(t|X = x) = \exp \left\{ -\Lambda_3(t)e^{\beta_{T_2} + \gamma_{T_2}^T x} \right\} - 1 + \int_0^t \lambda_1(m)e^{\beta_{M_2} + \gamma_{M_2}^T x} \times \exp \left\{ -\Lambda_1(m)e^{\beta_{M_2} + \gamma_{M_2}^T x} \right\} \left[ 1 - \exp \left\{ -\Lambda_2(t-m)e^{\beta_{R_2} + \gamma_{R_2}^T x} \right\} \right] \, dm
\]

and

\[
TE_3(t|X = x) = \exp \left\{ -\Lambda_3(t)e^{\beta_{T_3} + \gamma_{T_3}^T x} \right\} - \exp \left\{ -\Lambda_3(t)e^{\gamma_{T_3}^T x} \right\},
\]

where \( \Lambda_3(t) = \int_0^t \lambda_3(s) \, ds \).

As in [Yu et al. (2015)](http://example.com), we consider a multinomial logistic regression model on the stratum membership. In particular, we assume

\[
w_1(x; \alpha) = \Pr(U = 1|X = x) = \frac{\exp (\alpha_1^T \tilde{x})}{1 + \exp (\alpha_1^T \tilde{x}) + \exp (\alpha_2^T \tilde{x})},
\]

\[
w_2(x; \alpha) = \Pr(U = 2|X = x) = \frac{\exp (\alpha_2^T \tilde{x})}{1 + \exp (\alpha_1^T \tilde{x}) + \exp (\alpha_2^T \tilde{x})},
\]

and \( w_3(x; \alpha) = \Pr(U = 3|X = x) = \{1 + \exp (\alpha_1^T \tilde{x}) + \exp (\alpha_2^T \tilde{x})\}^{-1} \), where \( \alpha = (\alpha_1^T, \alpha_2^T)^T \) and \( \tilde{x} = (1, x^T)^T \). Then, the marginalized stratum-specific natural indirect and direct effects are given by

\[
NIE_1(t) = \Pr\{T(1, M(1)) \geq t|U = 1\} - \Pr\{T(1, M(0)) \geq t|U = 1\} = \frac{\int NIE_1(t|X = x)w_1(x; \alpha)dF(x)}{\int w_1(x; \alpha)dF(x)}
\]

and

\[
NDE_1(t) = \Pr\{T(1, M(0)) \geq t|U = 1\} - \Pr\{T(0, M(0)) \geq t|U = 1\} = \frac{\int NDE_1(t|X = x)w_1(x; \alpha)dF(x)}{\int w_1(x; \alpha)dF(x)}
\]

where \( F(\cdot) \) is the cumulative distribution function of \( X \).
2.5. Nonparametric Maximum Likelihood Estimation

For a random sample of \( n \) subjects, the observed semi-competing risks data are given by
\[
\mathcal{O} = \{ \mathcal{O}_i : i = 1, \ldots, n \},
\]
where
\[
\mathcal{O}_i = \{ \Delta_i^M, Z_i, \Delta_i^T, Y_i, A_i, X_i \}.
\]

For \( i = 1, \ldots, n \), if \( \Delta_i^M = 1 \), then the likelihood corresponding to subject \( i \) is given by
\[
\tilde{L}_{i1}(\mathcal{O}_i) = \Pr (U_i = 1 | X_i) \Pr \left( Z_i, Y_i, \Delta_i^T | U_i = 1, X_i, A_i \right)
+ I (A_i = 0) \Pr (U_i = 2 | X_i) \Pr \left( Z_i, Y_i, \Delta_i^T | U_i = 2, X_i, A_i = 0 \right);
\]
if \( \Delta_i^M = 0 \) and \( \Delta_i^T = 1 \), then the likelihood corresponding to subject \( i \) is given by
\[
\tilde{L}_{i2}(\mathcal{O}_i) = \Pr (U_i = 3 | X_i) \Pr \left( Y_i, \Delta_i^T | U_i = 3, X_i \right)
+ I (A_i = 1) \Pr (U_i = 2 | X_i) \Pr \left( Y_i, \Delta_i^T | U_i = 2, X_i, A_i = 1 \right);
\]
and if \( \Delta_i^M = \Delta_i^T = 0 \), then the likelihood corresponding to subject \( i \) is given by
\[
\tilde{L}_{i3}(\mathcal{O}_i) = \Pr (U_i = 1 | X_i) \Pr \left( Z_i, \Delta_i^M, Y_i, \Delta_i^T | U_i = 1, X_i \right)
+ \Pr (U_i = 2 | X_i) \{ I (A_i = 0) \Pr \left( Z_i, \Delta_i^M, Y_i, \Delta_i^T | U_i = 2, X_i, A_i = 0 \right)
+ I (A_i = 1) \Pr \left( Y_i, \Delta_i^T | U_i = 2, X_i, A_i = 1 \right) \}
+ \Pr (U_i = 3 | X_i) \Pr \left( Y_i, \Delta_i^T | U_i = 3, X_i \right) .
\]

Therefore, the likelihood function for the observed data \( \mathcal{O} \) is given by
\[
\prod_{i=1}^{n} \tilde{L}_{i1}(\mathcal{O}_i)^{\Delta_i^M} \left\{ \tilde{L}_{i2}(\mathcal{O}_i)^{\Delta_i^T} \tilde{L}_{i3}(\mathcal{O}_i)^{1-\Delta_i^T} \right\}^{1-\Delta_i^M}.
\]

We consider the nonparametric maximum likelihood estimation such that the estimators for \( \Lambda_1 \), \( \Lambda_2 \), and \( \Lambda_3 \) are step functions. In particular, let \( 0 < t_{11} < \cdots < t_{1m_1} < \infty \) be the ordered sequence of event times \( Z_i \)'s with \( \Delta_i^M = 1 \); let \( 0 < t_{21} < \cdots < t_{2m_2} < \infty \) be the
ordered sequence of gap times \( V_i \equiv Y_i - Z_i \)'s with \( \Delta_i^M = \Delta_i^T = 1 \); and let \( 0 < t_{31} < \cdots < t_{3m_3} < \infty \) be the ordered sequence of event times \( Y_i \)'s with \( \Delta_i^M = 0 \) and \( \Delta_i^T = 1 \). Let \( \lambda_{kl} \) be the jump size for \( \Lambda_k \) at \( t_{kl} \) for \( k = 1, 2, 3 \) and \( l = 1, \ldots, m_k \). Write \( \eta_{M1} = (\beta_{M1}, \gamma_{M1})^T \), \( \eta_{R1} = (\beta_{R1}, \gamma_{R1})^T \), \( \eta_{M2} = (\beta_{M2}, \gamma_{M2})^T \), \( \eta_{R2} = (\beta_{R2}, \gamma_{R2})^T \), \( \eta_{T2} = (\beta_{T2}, \gamma_{T2})^T \), \( \eta_{T3} = (\beta_{T3}, \gamma_{T3})^T \), \( \theta = (\eta_{M1}^T, \eta_{R1}^T, \eta_{M2}^T, \eta_{R2}^T, \eta_{T2}^T, \eta_{T3}^T, \alpha^T)^T \), and \( A = (\Lambda_1, \Lambda_2, \Lambda_3)^T \). We maximize the objective function

\[
L_n(\theta, A) = \prod_{i=1}^{n} L_{i1}(\theta, A)^{\Delta_i^M} \{ L_{i2}(\theta, A)^{\Delta_i^T} L_{i3}(\theta, A)^{1-\Delta_i^T} \}^{1-\Delta_i^M},
\]

where

\[
L_{i1}(\theta, A) = w_1(X_i; \alpha) \Lambda_1 \{ Z_i \} e^{\eta_{M1}^T w_i} \exp \left( -e^{\eta_{M1}^T w_i} \sum_{t_{1l} \leq Z_i} \lambda_{1l} \right)
\]

\[
\times \left( \Lambda_2 \{ V_i \} e^{\eta_{R1}^T w_i} \right)^{\Delta_i^T} \exp \left( -e^{\eta_{R1}^T w_i} \sum_{t_{2l} \leq V_i} \lambda_{2l} \right)
\]

\[
+ I(A_i = 0) w_2(X_i; \alpha) \Lambda_1 \{ Z_i \} e^{\eta_{M2}^T \tilde{x}_i} \exp \left( -e^{\eta_{M2}^T \tilde{x}_i} \sum_{t_{1l} \leq Z_i} \lambda_{1l} \right)
\]

\[
\times \left( \Lambda_2 \{ V_i \} e^{\eta_{R2}^T \tilde{x}_i} \right)^{\Delta_i^T} \exp \left( -e^{\eta_{R2}^T \tilde{x}_i} \sum_{t_{2l} \leq V_i} \lambda_{2l} \right),
\]

\[
L_{i2}(\theta, A) = I(A_i = 1) w_2(X_i; \alpha) \left( \Lambda_3 \{ Y_i \} e^{\eta_{T2}^T \tilde{x}_i} \right)^{\Delta_i^T} \exp \left( -\sum_{t_{3l} \leq Y_i} \lambda_{3l} e^{\eta_{T2}^T \tilde{x}_i} \right)
\]

\[
+ w_3(X_i; \alpha) \left( \Lambda_3 \{ Y_i \} e^{\eta_{T3}^T w_i} \right)^{\Delta_i^T} \exp \left( -\sum_{t_{3l} \leq Y_i} \lambda_{3l} e^{\eta_{T3}^T w_i} \right),
\]

\[
L_{i3}(\theta, A) = L_{i2}(\eta, A) + w_1(X_i; \alpha) \exp \left( -\sum_{t_{1l} \leq Z_i} \lambda_{1l} e^{\eta_{M1}^T w_i} \right)
\]

\[
+ I(A_i = 0) w_2(X_i; \alpha) \exp \left( -\sum_{t_{1l} \leq Z_i} \lambda_{1l} e^{\eta_{M2}^T \tilde{x}_i} \right),
\]

\[
W_i = (A_i, X_i^T)^T, \text{ and } \Lambda_k \{ t \} \text{ is the jump size of } \Lambda_k \text{ at time } t \text{ for } k = 1, 2, 3.
\]

By treating \( U_i \) \((i = 1, \ldots, n)\) as missing data, we propose an EM algorithm to maximize this objective function. The details of the EM algorithm are given in Appendix B. We
write \((\hat{\theta}, \hat{A})\) as the estimators. The indirect and direct effects in stratum with \(U = 1\) can then be estimated by

\[
\hat{\text{NIE}}_1(t; \mathbf{x}) = \sum_{t_{1j} \leq t} \left[ \exp \left( - \sum_{t_{2k} \leq t - t_{1j}} \hat{\lambda}_{2k} e^{\hat{\theta}_{R1} \hat{x}} \right) \right] \hat{\lambda}_{1j} \\
\times \left\{ e^{\hat{\theta}_{M1} \hat{x}} \exp \left( - \sum_{k=1}^{j} \hat{\lambda}_{1k} e^{\hat{\theta}_{M1} \hat{x}} \right) - e^{\hat{\gamma}_{M1} \hat{x}} \exp \left( - \sum_{k=1}^{j} \hat{\lambda}_{1k} e^{\hat{\gamma}_{M1} \hat{x}} \right) \right\} \\
+ \exp \left( - \sum_{t_{1j} \leq t} \hat{\lambda}_{1j} e^{\hat{\theta}_{M1} \hat{x}} \right) - \exp \left( - \sum_{t_{1j} \leq t} \hat{\lambda}_{1j} e^{\hat{\gamma}_{M1} \hat{x}} \right)
\]

(5)

and

\[
\hat{\text{NDE}}_1(t; \mathbf{x}) = \sum_{t_{1j} \leq t} \left[ \exp \left( - \sum_{t_{2k} \leq t - t_{1j}} \hat{\lambda}_{2k} e^{\hat{\theta}_{M1} \hat{x}} \right) - \exp \left( - \sum_{t_{2k} \leq t - t_{1j}} \hat{\lambda}_{2k} e^{\hat{\gamma}_{M1} \hat{x}} \right) \right] \times \hat{\lambda}_{1j} e^{\hat{\gamma}_{M1} \hat{x}} \exp \left( - \sum_{k=1}^{j} \hat{\lambda}_{1k} e^{\hat{\gamma}_{M1} \hat{x}} \right).
\]

(6)

The total effects in strata with \(U = 2\) and \(U = 3\) can be estimated by

\[
\hat{T}\text{E}_2(t; \mathbf{x}) = \exp \left( - \sum_{t_{1j} \leq t} \hat{\lambda}_{1j} e^{\hat{\theta}_{M1} \hat{x}} \right) - 1 \\
+ \sum_{t_{1j} \leq t} \left[ \hat{\lambda}_{1j} e^{\hat{\theta}_{M1} \hat{x}} \exp \left( - \sum_{k=1}^{j} \hat{\lambda}_{1k} e^{\hat{\theta}_{M1} \hat{x}} \right) \right] \left\{ 1 - \exp \left( - \sum_{t_{2k} \leq t - t_{1j}} \hat{\lambda}_{2k} e^{\hat{\theta}_{R2} \hat{x}} \right) \right\}
\]

(7)

and

\[
\hat{T}\text{E}_3(t; \mathbf{x}) = \exp \left( - \sum_{t_{1j} \leq t} \hat{\lambda}_{1j} e^{\hat{\theta}_{M1} \hat{x}} \right) - \exp \left( - \sum_{t_{1j} \leq t} \hat{\lambda}_{1j} e^{\hat{\gamma}_{M1} \hat{x}} \right).
\]

(8)

The marginalized stratum-specific indirect and direct effects in stratum with \(U = 1\) can be estimated by

\[
\hat{\text{NIE}}_1(t) = \sum_{i=1}^{n} \frac{w_1(X_i; \hat{\alpha}) \hat{\text{NIE}}_1(t; X_i)}{w_1(X_i; \hat{\alpha})}
\]

(9)

and

\[
\hat{\text{NDE}}_1(t) = \sum_{i=1}^{n} \frac{w_1(X_i; \hat{\alpha}) \hat{\text{NDE}}_1(t; X_i)}{w_1(X_i; \hat{\alpha})},
\]

(10)

respectively.
2.6. Asymptotic Properties

We study the asymptotic properties of the estimators under the semiparametric model in Section 2.4. Under suitable regularity conditions, the estimators \( \hat{\theta}, \hat{A} \) has the usual large sample properties, including consistency and asymptotic normality, as given in Theorem 3 below. Let \( \theta_0, \Lambda_{10}, \Lambda_{20}, \text{and } \Lambda_{30} \) be the true values of \( \theta, \Lambda_1, \Lambda_2, \text{and } \Lambda_3, \) respectively, \( \| \cdot \| \) be the Euclidean norm, and \( \tau_k \) be the upper limit of the support of \( \hat{\Lambda}_k \) for \( k = 1, 2, 3. \)

**Theorem 3.** Under regularity conditions,

\[
\| \hat{\theta} - \theta_0 \| + \sum_{k=1}^{3} \sup_{t \in [0, \tau_k]} \left| \hat{\Lambda}_k(t) - \Lambda_{k0}(t) \right|
\]

converges to zero almost surely. In addition, \( \sqrt{n}(\hat{\theta} - \theta_0, \hat{\Lambda}_1(\cdot) - \Lambda_{10}(\cdot), \hat{\Lambda}_2(\cdot) - \Lambda_{20}(\cdot), \hat{\Lambda}_3(\cdot) - \Lambda_{30}(\cdot)) \) converges weakly to a zero-mean Gaussian process in the Banach space \( \mathbb{R}^m \times l^\infty(A_1) \times l^\infty(A_2) \times l^\infty(A_3), \) where \( m \) is the dimension of \( \theta \) and \( A_k \) is the unit ball in the space of functions on \( [0, \tau_k] \) with bounded variation for \( k = 1, 2, 3. \)

**Theorem 4.** Under regularity conditions, the estimators for stratum-specific effects given in (5)-(10) are consistent and asymptotically normal.

Since the form of the limiting variances of the stratum-specific effects is complicated, we estimate the variance of the estimators by a nonparametric bootstrap procedure in all numerical studies.

3. Simulation Studies

We conducted simulation studies to examine the performance of the proposed methods. We generated two covariates \( X_1 \sim N(0, 1) \) and \( X_2 \sim Unif(0, 1) \) and generated the treatment indicator \( A \sim Bin(0.5) \) to reflect 1:1 randomization. We set \( \Lambda_1(t) = t, \Lambda_2(t) = 0.2t, \) and \( \Lambda_3(t) = \log(1 + t), \) while the true values of the other parameters are shown in Table
along with the simulation results. We generated a censoring time $C \sim \text{Unif}(0, 15)$ to obtain approximately 51% and 26% censoring rates for the nonterminal and terminal events, respectively. The proportions of subjects with $U = 1, 2, 3$ are approximately 31%, 41%, and 28%, respectively.

We considered 1000 replicates with sample sizes $n = 1000$ and 2000, where 100 bootstrap samples were used for variance estimation. Table 1 shows the simulation results, where Bias, SE and SEE denote, respectively, the averaged bias, empirical standard error and averaged standard error estimates, and CP stands for the empirical coverage probability of the 95% confidence intervals. All examined replications converge with a $10^{-6}$ convergence criterion. The parameter estimators are virtually unbiased. The bootstrap variance estimator overestimates the true variability for some of the parameters, but it gets more accurate when sample size increases.

The estimators for the baseline cumulative hazard functions only take jump till the last observation times, such that the estimates after the last observation time is not meaningful. Therefore, to summarize the performance of the baseline hazard estimators, for every time point $t$, we only consider the replicates with last observation time greater than $t$. Figure 1 shows the median of the estimated baseline hazard functions, among such replicates. We plot till the time point at which at least 800 replicates have meaningful estimates. The bias gets smaller as sample size increases.

Table 2 shows the performance of the estimated stratum-specific indirect and direct effects in stratum with $U = 1$ and $X = (0.5, 0.5)^T$, as well as the estimated total effects for strata with $U = 2, 3$ and the same covariate values. Similarly, for any $t$ the average was taken over all the replicates with estimators that have last jump time no less than $t$. The bias gets smaller as sample size increases. The variance estimator is accurate and the coverage probability is close to the nominal level when sample size is large.
Table 1. Simulation Results for Regression Parameters

| Value | Bias | SE  | SEE | CP      | Bias  | SE  | SEE | CP      |
|-------|------|-----|-----|---------|-------|-----|-----|---------|
| $\beta_{M1}$ | 0.5 | 0.008 | 0.224 | 0.261 | 0.97 | 0.006 | 0.147 | 0.168 | 0.97 |
| $\gamma_{M1}$ | 0.5 | 0.010 | 0.091 | 0.095 | 0.96 | 0.005 | 0.063 | 0.063 | 0.94 |
| $\beta_{R1}$ | 0.5 | -0.043 | 0.276 | 0.334 | 0.97 | -0.025 | 0.161 | 0.202 | 0.97 |
| $\gamma_{R1}$ | -0.2 | -0.011 | 0.095 | 0.102 | 0.96 | -0.004 | 0.065 | 0.067 | 0.95 |
| $\beta_{R2}$ | 0.4 | -0.068 | 0.586 | 0.699 | 0.97 | -0.028 | 0.358 | 0.435 | 0.96 |
| $\gamma_{R2}$ | 0.5 | -0.013 | 0.187 | 0.230 | 0.96 | -0.002 | 0.115 | 0.138 | 0.97 |
| $\beta_{T2}$ | 0.0 | 0.028 | 0.485 | 0.523 | 0.98 | 0.012 | 0.357 | 0.359 | 0.96 |
| $\gamma_{T2}$ | -0.5 | 0.015 | 0.175 | 0.197 | 0.98 | 0.012 | 0.124 | 0.132 | 0.97 |
| $\beta_{T3}$ | 0.2 | -0.044 | 0.410 | 0.448 | 0.98 | -0.034 | 0.334 | 0.332 | 0.96 |
| $\gamma_{T3}$ | -0.2 | -0.035 | 0.107 | 0.118 | 0.95 | -0.024 | 0.076 | 0.078 | 0.95 |
| $\alpha_1$ | 0.0 | 0.009 | 0.199 | 0.213 | 0.96 | 0.010 | 0.148 | 0.146 | 0.95 |
| $\alpha_2$ | 0.2 | 0.025 | 0.296 | 0.321 | 0.96 | 0.010 | 0.201 | 0.211 | 0.96 |

NOTE: Bias, SE and SEE denote, respectively, the mean bias, empirical standard error and mean standard error estimator. CP stands for the empirical coverage probability of the 95% confidence interval.
Table 2. Simulation Results for Stratum-Specific Mediation Effects and Total Effects

| NDE_1 | 2    | -0.11 | 0.014 | 0.056 | 0.070 | 0.97 | 0.007 | 0.031 | 0.041 | 0.97 |
|-------|------|-------|-------|-------|-------|------|-------|-------|-------|------|
|       | 4    | -0.17 | 0.018 | 0.090 | 0.106 | 0.96 | 0.010 | 0.052 | 0.066 | 0.97 |
|       | 6    | -0.18 | 0.020 | 0.096 | 0.107 | 0.94 | 0.010 | 0.057 | 0.069 | 0.96 |

| NIE_1 | 2    | -0.04 | -0.001| 0.022 | 0.025 | 0.97 | 0.000 | 0.015 | 0.017 | 0.97 |
|-------|------|-------|-------|-------|-------|------|-------|-------|-------|------|
|       | 4    | -0.03 | -0.001| 0.016 | 0.018 | 0.97 | -0.001| 0.011 | 0.012 | 0.96 |
|       | 6    | -0.02 | -0.001| 0.010 | 0.011 | 0.97 | 0.000 | 0.007 | 0.007 | 0.96 |

| TE_2  | 2    | -0.10 | -0.036| 0.158 | 0.175 | 0.97 | -0.022| 0.115 | 0.126 | 0.97 |
|-------|------|-------|-------|-------|-------|------|-------|-------|-------|------|
|       | 4    | 0.10  | -0.046| 0.159 | 0.180 | 0.96 | -0.026| 0.113 | 0.127 | 0.97 |
|       | 6    | 0.17  | -0.047| 0.136 | 0.156 | 0.97 | -0.027| 0.097 | 0.109 | 0.97 |
|       | 8    | 0.18  | -0.044| 0.115 | 0.131 | 0.96 | -0.025| 0.084 | 0.093 | 0.96 |

| TE_3  | 2    | -0.07 | 0.021 | 0.139 | 0.147 | 0.97 | 0.015 | 0.117 | 0.114 | 0.95 |
|-------|------|-------|-------|-------|-------|------|-------|-------|-------|------|
|       | 4    | -0.06 | 0.031 | 0.119 | 0.126 | 0.98 | 0.022 | 0.101 | 0.099 | 0.96 |
|       | 6    | -0.06 | 0.033 | 0.101 | 0.107 | 0.97 | 0.024 | 0.086 | 0.085 | 0.96 |
|       | 8    | -0.05 | 0.033 | 0.088 | 0.093 | 0.97 | 0.024 | 0.075 | 0.074 | 0.96 |

NOTE: Bias, SE and SEE denote, respectively, the mean bias, empirical standard error and mean standard error estimator. CP stands for the empirical coverage probability of the 95% confidence interval.
Figure 1. Performance of the estimated baseline cumulative hazard functions.

4. Application

We consider application of the proposed methods to a prostate cancer clinical trial. NCIC Clinical Trials Group PR.3/Medical Research Council PR07/Intergroup T94-0110 is a randomized controlled trial of patients with locally advanced prostate cancer. The primary objective is to determine whether the addition of radiotherapy (RT) to androgen-deprivation therapy (ADT) prolonged overall survival, defined as time from random assignment to death from any cause. One thousand two hundred and five patients with locally advanced prostate cancer were recruited and randomly assigned between 1995 and 2005, 602 to ADT alone and 603 to ADT + RT. These patients were either with T3-4, N0/Nx, M0 prostate cancer or with T1-2 disease with either prostate-specific antigen (PSA) of more than 40µg/L or PSA of 20 to 40µg/L plus Gleason score of 8 to 10. In the final report of the study (Mason et al., 2015), at a median follow-up time of 8 years, 465 patients had died. Overall survival was significantly improved in the patients allocated to ADT + RT (hazard ratio 0.70 with 95% CI, 0.57 to 0.85; P < .001).

In addition to the primary outcome of death, the study also collected data on time to
disease progression, which was defined as the first of any of the following events: biochemical progression, local progression, or development of metastatic disease. We analyzed the data to reveal the proportions of the treatment effect on overall survival that are mediated by disease progression. Particularly, we adjusted for initial PSA level (< 20 vs. 20 to 50, vs. >50 g/L) and Gleason score (8 vs. 8 to 10).

We analyzed the data using the proposed approach, with 100 bootstrap samples for variance estimation. The parameter estimates for regression coefficients for the event time processes are shown in Table 3. For stratum with $U = 1$, ADT + RT is associated with a decreased risk of disease progression, while it is associated with an increased risk from disease progression to death. For stratum with $U = 3$, ADT + RT is associated with a decreased risk of death. The effects are not significant at 0.05 level. For stratum with $U = 1$, a subject with initial PSA level >50 g/L is associated with significantly increased risk of disease progression, compared to a similar subject with initial PSA level <20 g/L; and a subject with Gleason score 8-10 is associated with significantly decreased risk of disease progression, compared to a similar subject with Gleason score <8.

Table 4 shows the parameter estimators of the logistic regression model for stratum membership. By averaging over the stratum membership probabilities over all subjects given their covariate values, the average probabilities of belong to strata $U = 1, 2,$ and 3 are 40.1%, 25.7%, and 34.2%, respectively. To verify if the model is reasonable, we estimated the stratum-specific survival functions for every subject and summarize the subject-specific survival function by weighting them by his/her stratum membership probabilities. We average the estimated survival functions for subjects assigned to ADT+RT versus ADT, and plot them against the survival function estimators from the Kaplan Meier methods and the proportional hazards model. The results are shown in Figure 2. The estimated population-average survival functions for ADT+RT and ADT groups are similar to those from the Kaplan Meier methods and the proportional hazards model, especially for time
Table 3. Parameter Estimates for Regression Coefficients for Event Time Processes

| Process                        | $U = 1$          |           | $U = 2$, ADT |           | $U = 2$, ADT + DT |           | $U = 3$          |
|--------------------------------|------------------|------------|-------------|------------|------------------|------------|------------------|
|                                |                  | Health → Diseas | Disease → Death | Est   | SEE | p-value | Est   | SEE | p-value | Est   | SEE | p-value | Est   | SEE | p-value |
| ADT + RT                      | −0.825           | 0.987      | 0.403       | 0.460           | 0.658         | 0.484       |           |
| Initial PSA Level (20 to 50 g/L)| 0.321           | 0.530      | 0.545       | −0.097          | 0.305         | 0.751       |           |
| Initial PSA Level (> 50 g/L)   | 1.607           | 0.566      | 0.005       | 0.065           | 0.342         | 0.848       |           |
| Gleason Score (8-10)           | −2.008           | 0.413      | 0.0000      | −0.378          | 0.241         | 0.117       |           |
| Intercept                      | −1.917           | 1.587      | 0.227       | −0.557          | 3.548         | 0.875       |           |
| Initial PSA Level (20 to 50 g/L)| 0.663           | 1.005      | 0.510       | −0.304          | 0.863         | 0.725       |           |
| Initial PSA Level (> 50 g/L)   | 1.619           | 0.904      | 0.073       | −0.104          | 0.940         | 0.912       |           |
| Gleason Score (8-10)           | 0.674           | 0.952      | 0.479       | −0.106          | 3.381         | 0.975       |           |
Table 4. Parameter Estimates for Regression Coefficients for Stratum Membership

|                      | $\alpha_1$ |         |         | $\alpha_2$ |         |         |
|----------------------|------------|---------|---------|------------|---------|---------|
|                      | Est       | SEE     | p-value | Est        | SEE     | p-value |
| Intercept            | 0.205     | 0.441   | 0.643   | 0.291      | 0.743   | 0.695   |
| Initial PSA Level (20 to 50 g/L) | 0.090    | 0.583   | 0.877   | 0.625      | 1.054   | 0.553   |
| Initial PSA Level (> 50 g/L) | −0.684   | 0.517   | 0.186   | 0.004      | 0.929   | 0.996   |
| Gleason Score (8-10) | 0.134     | 0.415   | 0.746   | −1.495     | 0.732   | 0.041   |

before 10 years when data are not sparse, indicating proper fit of the proposed approach.

Figure 3 shows the estimated marginalized stratum-specific indirect and direct effects (with 95% confidence intervals) for stratum with $U = 1$. The estimated natural indirect effect is positive and increasing over time, and the estimated natural direct effect is slightly negative over time. However, the 95% confidence intervals are wide such that the stratum-specific natural indirect and direct effects are not significant different from zero. The total effect in stratum with $U = 1$ is positive and increasing over time, corresponding to an increased survival probability assigned to ADT+RT versus ADT in stratum with $U = 1$.

It is worth noting that the primary analysis for the data shows that overall survival was significantly improved in the patients allocated to ADT + RT compared to ADT. However, our analysis failed to obtain a significant stratum-specific overall effect of ADT + RT. The main reason is that by identifying subjects to different strata, the sample size to estimate parameters in each stratum is much smaller than that for the proportional hazards model based on all available subjects. In addition, the proposed model has much more parameters, such that the variability for parameter estimation significantly increases.
Figure 2. *Estimated survival functions from the proposed, Kaplan-Meier, and proportional hazards model approaches.*
Figure 3. Estimated stratum-specific indirect and direct effects in stratum with $U = 1$. 
5. Discussion

Semi-competing risks data are frequently observed in medical studies, where the terminal event time may censor the intermediate event time but not vice versa. To define and estimate causal contrasts of the effect of a treatment to the terminal and intermediate events, we introduced a novel principal stratification framework that distinguishes susceptible and non-susceptible subjects given different treatments, and defined the natural indirect and direct effects in the stratum where the times to intermediate and terminal events are well-defined given both treatments. We provided reasonable assumptions to identify the stratum-specific natural indirect and direct effects, proposed a semiparametric model, and studied an EM algorithm to obtain the nonparametric maximum likelihood estimators of model parameters. We showed that the estimators are consistent and asymptotically efficient estimated under mild regularity conditions, and their performance are satisfactory in finite sample numerical studies.

In identifying the stratum-specific natural indirect and direct effects, we assumed that there are no subjects who are susceptible to the intermediate event under treatment \((A = 1)\) and non-susceptible under control \((A = 0)\). This assumption may need careful examination based on scientific understanding of how treatment may affect the intermediate event. In our data application, we assessed this assumption by fitting the proposed model with switched treatment indicator labels of ADT+RT and ADT. The estimated probability of belonging to stratum with \(U = 2\) (equivalent to the fourth stratum in the original labeling) is very low, suggesting that the assumption on non-existence of the fourth stratum may be valid. In some applications, this fourth stratum may indeed exist. In the literature of principal stratification for uncensored data with four or more strata, the effect of interest often can only be interval identified. Interval identification with a regression model often results in a complicated solution manifold, with properties often not well understood. We
plan to explore this problem in a future study.

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APPENDIX A Identification of Stratum-Specific Effects

A.1 Proof of Theorem 1

Note that (3) in Assumption 2 implies

\[ T(a,m) \perp A|M(a^*) = m^*, X, U = 1. \]  \hspace{1cm} (A.1)

In stratum \( U = 1 \), for a given \( t \leq \tau \) and any \( a, a^* \), we have

\[
\begin{align*}
\Pr\{T(a,M(a^*)) \geq t | X = x, U = 1\} &= \Pr\{T(a,m) \geq t | M(a^*) = m, X = x, U = 1\} dF_{M(a^*)|X=x,U=1}(m) \\
&= \int \Pr\{T(a,m) \geq t | M(a^*) = m, A = a^*, X = x, U = 1\} dF_{M(a^*)|X=x,U=1}(m) \\
&= \int \Pr\{T(a,m) \geq t | A = a^*, X = x, U = 1\} dF_{M(a^*)|X=x,U=1}(m) \\
&= \int \Pr\{T(a,m) \geq t | A = a, X = x, U = 1\} dF_{M(a^*)|X=x,U=1}(m)
\end{align*}
\]
\[
\int \Pr\{T(a, m) \geq t| M(a) = m, A = a, X = x, U = 1\}dF_{M(a^*)|X=x,U=1}(m)
\]
\[
= \int \Pr\{T(a, m) \geq t| M(a) = m, A = a, X = x, U = 1\}dF_{M(a^*)|X=x,U=1}(m)
\]
\[
+ \int_{t}^{\infty} \Pr\{T(a, m) \geq t| M(a) = m, A = a, X = x, U = 1\}dF_{M(a^*)|X=x,U=1}(m)
\]
\[
= \int \Pr\{T(a, m) \geq t| M(a) = m, A = a, X = x, U = 1\}dF_{M(a^*)|X=x,U=1}(m)
\]
\[
+ \Pr(M(a^*) \geq t| X = x, U = 1),
\]

where the second equality follows from (A.1), the third and fifth equalities follow from (4) in Assumption 2, and the last equality follows from the fact that \(T(a, m) \geq t\) with probability one for any \(m \geq t\) given \(U = 1\). Then, following (3) in Assumption 2 and Assumption 1, the proceeding expression is equal to

\[
\int_{0}^{t} \frac{\Pr\{T(a) \geq t, M(a) = m| A = a, X = x, U = 1\}}{\Pr\{M(a) = m| A = a, X = x, U = 1\}}dF_{M(a^*)|A=a^*,X=x,U=1}(m)
\]
\[
+ \Pr(M(a^*) \geq t| A = a^*, X = x, U = 1)
\]
\[
= \int_{0}^{t} \Pr(T \geq t| M = m, A = a, X = x, U = 1)dF_{M|A=a^*,X=x,U=1}(m)
\]
\[
+ \Pr(M > t| A = a^*, X = x, U = 1).
\]

Then, the natural indirect and direct effects, as defined in equations (1) and (2), are equal to

\[
NIE_1(t; x) = \int_{0}^{t} \Pr(T \geq t| M = m, A = 1, X = x, U = 1)
\]
\[
\times \left\{dF_{M|A=1,X=x,U=1}(m) - dF_{M|A=0,X=x,U=1}(m)\right\}
\]
\[
+ \Pr(M > t| A = 1, X = x, U = 1) - \Pr(M > t| A = 0, X = x, U = 1)
\]

and

\[
NDE_1(t; x) = \int_{0}^{t} \{\Pr(T \geq t| M = m, A = 1, X = x, U = 1)
\]
\[-\Pr(T \geq t|M = m, A = 0, X = x, U = 1)} dF_{M|A=0,X=x,U=1}(m).

For stratum with \(U = 2\), we have

\[TE_2(t; x) = \Pr(T(1) \geq t|A = 1, X = x, U = 2) - \Pr(T(0) \geq t|A = 0, X = x, U = 2) = \Pr(T \geq t|A = 1, X = x, U = 2) - \Pr(T \geq t|A = 0, X = x, U = 2),\]

where the two equalities follow from Assumptions 2 and 1, respectively. Similarly, for stratum with \(U = 3\), we have

\[TE_3(t; x) = \Pr(T(1) \geq t|A = 1, X = x, U = 3) - \Pr(T(0) \geq t|A = 0, X = x, U = 3) = \Pr(T \geq t|A = 1, X = x, U = 3) - \Pr(T \geq t|A = 0, X = x, U = 3),\]

A.2 Proof of Theorem 2

We first consider the identification of stratum membership probabilities, as the first step to identify the stratum-specific effects. By the definition of the strata, we have

\[\Pr(M < \infty|A = 0, X = x) = \Pr(M(0) < \infty|A = 0, X = x) = \Pr(M(0) < \infty, M(1) < \infty|A = 0, X = x) + \Pr(M(0) < \infty, M(1) = \infty|A = 0, X = x) = \Pr(U = 1|A = 0, X = x) + \Pr(U = 2|A = 0, X = x) = \Pr(U = 1|X = x) + \Pr(U = 2|X = x),\]

where the last equality follows from Assumption 3. Similarly, we have the following equalities:

\[\Pr(M < \infty|A = 1, X = x) = \Pr(U = 1|X = x)\]
\[\Pr(M = \infty|A = 0, X = x) = \Pr(U = 3|X = x)\]
\[\Pr(M = \infty|A = 1, X = x) = \Pr(U = 2|X = x) + \Pr(U = 3|X = x).\]
Therefore, the stratum membership probabilities \( \Pr(U = u|X) \) can be identified by the observed data if there is no censoring and we can observed if \( M = \infty \). The identification of the quantities in the presence of censoring is discussed in the end of the section.

We further consider the distributions of the (observed) intermediate and primary event times to identify terms in the definition of stratum-specific effects. First, consider the case if we observe \( M = m < \infty \) for a subject assigned to treatment \( A = 1 \). Since it implies \( M(1) < \infty \), this subject should have \( U = 1 \) with probability one. That is, for any \( m < \infty \),

\[
\Pr(M = m|A = 1, X = x) = \Pr(M = m, M(1) \leq T(1)|A = 1, X = x) \\
= \Pr(M = m, M(0) \leq T(0), M(1) \leq T(1)|A = 1, X = x) \\
= \Pr(M = m, U = 1|A = 1, X = x) \\
= \Pr(M = m|U = 1, A = 1, X = x) \Pr(U = 1|A = 1, X = x) \\
= \Pr(M(1) = m|X = x, U = 1) \Pr(U = 1|X = x),
\]

where the first equality follows from Assumption 1, the second and third equalities follow from the definition of strata, and last equality follows from Assumption 3. Similarly, we have for any \( m \leq t < \infty \),

\[
\Pr(T \geq t|M = m, A = 1, X = x) = \frac{\Pr(T < t, M = m|A = 1, X = x)}{\Pr(M = m|A = 1, X = x)} \\
= \frac{\Pr(T \geq t, M = m, M(1) \leq T(1)|A = 1, X = x)}{\Pr(M = m, M(1) \leq T(1)|A = 1, X = x)} \\
= \frac{\Pr(T \geq t, M = m, U = 1|A = 1, X = x)}{\Pr(M = m, U = 1|A = 1, X = x)} \\
= \Pr(T(1) \geq t|M(1) = m, X = x, U = 1).
\]

For the case that we observe \( M = m < \infty \) for a subject assigned to treatment \( A = 0 \), the subject would possibly have \( U = 1 \) or \( U = 2 \), since both strata has \( M(0) < \infty \). Then, we have

\[
\Pr(M = m|A = 0, X = x)
\]
\[ Pr(M = m, M(0) \leq T(0)|A = 0, X = x) \]
\[ = Pr(M = m, M(0) \leq T(0), M(1) \leq T(1)|A = 0, X = x) \]
\[ + Pr(M = m, M(0) \leq T(0), M(1) = \infty|A = 0, X = x) \]
\[ = Pr(M = m, U = 1|A = 0, X = x) + Pr(M = m, U = 2|A = 0, X = x) \]
\[ = Pr(M = m|A = 0, X = x, U = 1) Pr(U = 1|X = x) \]
\[ + Pr(M = m|A = 0, X = x, U = 2) Pr(U = 2|X = x) \]
\[ = Pr(M(0) = m|X = x, U = 1) Pr(U = 1|X = x) \]
\[ + g_1(Pr(M(0) = m|X = x, U = 1); x) Pr(U = 2|X = x), \]

where the last equality follows from Assumption 4, and

\[ Pr(T \geq t|M = m, A = 0, X = x) \]
\[ = \frac{Pr(T \geq t, M = m|A = 0, X = x)}{Pr(M = m|A = 0, X = x)} \]
\[ = \frac{Pr(T \geq t, M = m, M(0) \leq T(0)|A = 0, X = x)}{Pr(M = m|A = 0, X = x)} \]
\[ = \frac{\sum_{u=1,2} Pr(T(0) \geq t|M(0) = m, X = x, U = u) Pr(M(0) = m|X = x, U = u) Pr(U = u|X = x)}{\sum_{u=1,2} Pr(M = m(0)|X = x, U = u) Pr(U = u|X = x)}. \]

Then, the natural indirect effect can be presented as

\[ NIE_1(t; x) = \int_0^t Pr(T \geq t|M = m, A = 1, X = x) \]
\[ \times \{Pr(M = m|M < \infty, A = 1, X = x) - h_1^*(m; x)\} \ dm \]
\[ + Pr(M \leq t|M < \infty, A = 1, X = x) - \int_0^t h_1^*(m; x) dm. \]  

(A.2)

where \( h_1^*(m; x) \) is the solution to the equation

\[ Pr(M = m|A = 0, X = x) = h_1(m; x) \ Pr(M < \infty|A = 1, X = x) \]
\[ + g_1\{h_1(m; x); x\} \{Pr(M < \infty|A = 0, X = x) - Pr(M < \infty|A = 1, X = x)\}. \]
Similarly, the natural direct effect can be presented as

\[ NDE_1(t; x) = \int_0^t \{ \Pr(T \geq t|M = m, A = 1, X = x) - h_2^*(m, t; x) \} h_1^*(m; x) dm, \quad (A.3) \]

where \( h_2^*(m, t; x) \) is the solution to

\[ \Pr(T \geq t, M = m|A = 0, X = x) = h_2(m, t; x) h_1^*(m; x) \Pr(M < \infty|A = 1, X = x) \]

\[ + g_2 \{ h_2(m, t; x); x \} g_1 \{ h_1^*(m; x); x \} \]

\[ \times \{ \Pr(M < \infty|A = 0, X = x) - \Pr(M < \infty|A = 1, X = x) \}. \]

By similar derivations, we have

\[ \Pr(T \geq t, M = \infty|A = 1, X = x) = \Pr(T \geq t|A = 1, X = x, U = 2) \Pr(U = 2|X = x) \]

\[ + \Pr(T \geq t|A = 1, X = x, U = 3) \Pr(U = 3|X = x) \]

\[ = g_3 \{ \Pr(T(1) \geq t|X = x, U = 2) \} \Pr(U = 2|X = x) \]

\[ + \Pr(T(1) \geq t|X = x, U = 3) \Pr(U = 3|X = x), \]

and

\[ \Pr(T \geq t, M = \infty|A = 0, X = x) = \Pr(T(0) \geq t|X = x, U = 3) \Pr(U = 3|X = x). \]

Then, the stratum-specific total effects for strata with \( U = 2 \) and \( U = 3 \) are

\[ TE_2(t; x) = \int_0^t g_2 \{ h_2^*(m, t; x); x \} g_1 \{ h_1^*(m; x); x \} dm - g_3 \{ h_3^*(t; x); x \}, \quad (A.4) \]

and

\[ TE_3(t; x) = h_3^*(t; x) - \Pr(T \geq t|M = \infty, A = 0, X = x), \quad (A.5) \]

where \( h_3^*(t; x) \) is the solution to the equation

\[ \Pr(T = t, M < \infty|A = 1, X = x) = h_3(t; x) \Pr(M = \infty|A = 0, X = x) \]

32
\[ + g_3 \{ h_3(t; x); x \} \{ \Pr(M = \infty | A = 1, X = x) - \Pr(M = \infty | A = 0, X = x) \}. \]

In the special case that \( g_k(\cdot; x) \) are identity functions, i.e., the stratum-specific joint distributions of \( \{ M(0), T(0) \} \) are the same for strata \( U = 1 \) and \( U = 2 \) given \( X = x \), and the stratum-specific distributions of \( T(0) \) are the same for strata \( U = 2 \) and \( U = 3 \) given \( X = x \), the functions \( h_k^* \)'s have closed form

\[
\begin{align*}
    h_1^*(m; x) &= \Pr(M = m | M < \infty, A = 0, X = x), \\
    h_2^*(m, t; x) &= \Pr(T \geq t | M = m, A = 0, X = x), \\
    h_3^*(t; x) &= \Pr(T < t | M = \infty, A = 1, X = x).
\end{align*}
\]

Then, the stratum-specific effects can be identified by

\[
NIE_1(t; x) = \int_0^t \Pr(T \geq t | M = m, A = 1, X = x) \{ \Pr(M = m | M < \infty, A = 1, X = x) \\
- \Pr(M = m | M < \infty, A = 0, X = x) \} dm \\
+ \Pr(M \leq t | M < \infty, A = 1, X = x) - \Pr(M \leq t | M < \infty, A = 0, X = x),
\]

\[
NDE_1(t; x) = \int_0^t \{ \Pr(T \geq t | M = m, A = 1, X = x) - \Pr(T \geq t | M = m, A = 0, X = x) \} \\
\times \Pr(M = m | M < \infty, A = 0, X = x) dm,
\]

\[
TE_2(t; x) = \int_0^t \Pr(T \geq t, M = m | M < \infty, A = 1, X = x) dm \\
- \Pr(T \geq t | M = \infty, A = 0, X = x),
\]

and

\[
TE_3(t; x) = \Pr(T \geq t | M = \infty, A = 1, X = x) - \Pr(T \geq t | M = \infty, A = 0, X = x).
\]

In the presence of censoring, we cannot observe if \( M = \infty \), such that previous formula cannot be directly applied. However, we are still able to identify the quantities if we assume non-informative censoring and sufficient follow-up in strata (Assumption 5). Particularly,
we consider the marker process $I(M \leq t)$ along with the event time $T$. Then, based on an extension of results in Maller and Zhou (1992), the probability $\Pr(M = \infty | A, X)$ can be consistently estimated by the empirical value of the marker process at the last observed failure time. By replacing terms related to $\Pr(M = \infty | A, X)$ by their estimators, we identify the stratum-specific mediation effects and total effects.

APPENDIX B  Details on EM Algorithm

Based on the likelihood function with known $U_i$, we are then able to propose an EM algorithm treating $U_i (i = 1, \ldots, n)$ as missing data. In particular, the complete-data log-likelihood (with known $U_i$ for $i = 1, \ldots, n$) is given by

$$l_n(\beta, \gamma, \alpha, \Lambda) = \sum_{i=1}^{n} \left[ I(U_i = 1) \left\{ \alpha_1^T \tilde{X}_i + \Delta_i^M \left( \log \Lambda_1 \{Z_i\} + \eta_{M1}^T W_i - e^{\eta_{R1}^T W_i} \sum_{t_2 \leq V_i} \lambda_{2l} \right) 
+ \Delta_i^M \Delta_i^T \left( \log \Lambda_2 \{V_i\} + \eta_{R1}^T W_i \right) - (1 - \Delta_i^T + \Delta_i^M \Delta_i^T) e^{\eta_{R1}^T W_i} \sum_{t_2 \leq Z_i} \lambda_{2l} \right\} 
+ I(A_i = 0, U_i = 2) \left\{ \alpha_2^T \tilde{X}_i + \Delta_i^M \left( \log \Lambda_1 \{Z_i\} + \eta_{M2}^T \tilde{X}_i - e^{\eta_{R2}^T \tilde{X}_i} \sum_{t_2 \leq V_i} \lambda_{2l} \right) 
+ \Delta_i^M \Delta_i^T \left( \log \Lambda_2 \{V_i\} + \eta_{R2}^T \tilde{X}_i \right) - (1 - \Delta_i^T + \Delta_i^M \Delta_i^T) e^{\eta_{R2}^T \tilde{X}_i} \sum_{t_2 \leq Z_i} \lambda_{2l} \right\} 
+ I(A_i = 1, U_i = 2)(1 - \Delta_i^M) \left\{ \alpha_2^T \tilde{X}_i + \Delta_i^T \left( \log \Lambda_3 \{Y_i\} + \eta_{T2}^T \tilde{X}_i \right) - e^{\eta_{T2}^T \tilde{X}_i} \sum_{t_3 \leq Y_i} \lambda_{3l} \right\} 
+ I(U_i = 3)(1 - \Delta_i^M) \left\{ \Delta_i^T \left( \log \Lambda_3 \{Y_i\} + \eta_{T3}^T W_i \right) - e^{\eta_{T3}^T W_i} \sum_{t_3 \leq Y_i} \lambda_{3l} \right\} 
- \log \left\{ 1 + \exp \left( \alpha_1^T \tilde{X}_i \right) + \exp \left( \alpha_2^T \tilde{X}_i \right) \right\} \right] \right].$$
In the E-step of the EM algorithm, we evaluate the conditional expectation \( U_i \) for subjects \( i = 1, \ldots, n \). In particular,

\[
\widehat{\Pr}(U_i = 1) = \Delta_i^M \left\{ I(A_i = 1) + I(A_i = 0) \frac{B_{i1}}{B_{i1} + B_{i2}} \right\} + (1 - \Delta_i^M)(1 - \Delta_i^T) \frac{D_{i1}}{D_{i1} + D_{i2} + D_{i3}}
\]

\[
\widehat{\Pr}(U_i = 2) = \Delta_i^M I(A_i = 0) \frac{B_{i2}}{B_{i1} + B_{i2}} + (1 - \Delta_i^M) \Delta_i^T I(A_i = 1) \frac{C_{i2}}{C_{i2} + C_{i3}}
\]

\[
+ (1 - \Delta_i^M)(1 - \Delta_i^T) \frac{D_{i2}}{D_{i1} + D_{i2} + D_{i3}}
\]

\[
\widehat{\Pr}(U_i = 3) = (1 - \Delta_i^M) \Delta_i^T \left\{ I(A_i = 0) + I(A_i = 1) \frac{C_{i3}}{C_{i2} + C_{i3}} \right\}
\]

\[
+ (1 - \Delta_i^M)(1 - \Delta_i^T) \frac{D_{i3}}{D_{i1} + D_{i2} + D_{i3}}
\]

where

\[
B_{i1} = \exp \left\{ \alpha_i^T \tilde{X}_i + \eta_{M1}^T W_i + \Delta_i^T (\eta_{R1}^T W_i) - e^{\eta_{M1}^T W_i} \sum_{t_{11} \leq Z_i} \lambda_{1l} - e^{\eta_{R1}^T W_i} \sum_{t_{2l} \leq V_i} \lambda_{2l} \right\},
\]

\[
B_{i2} = \exp \left\{ \alpha_i^T \tilde{X}_i + \eta_{M2}^T \tilde{X}_i + \Delta_i^T (\eta_{R2}^T \tilde{X}_i) - e^{\eta_{M2}^T \tilde{X}_i} \sum_{t_{11} \leq Z_i} \lambda_{1l} - e^{\eta_{R2}^T \tilde{X}_i} \sum_{t_{2l} \leq V_i} \lambda_{2l} \right\},
\]

\[
C_{i2} = \exp \left( \alpha_i^T \tilde{X}_i + \eta_{R2}^T \tilde{X}_i - e^{\eta_{R2}^T \tilde{X}_i} \sum_{t_{3l} \leq Y_i} \lambda_{3l} \right),
\]

\[
C_{i3} = \exp \left( \eta_{R3}^T W_i - e^{\eta_{R3}^T W_i} \sum_{t_{3l} \leq Y_i} \lambda_{3l} \right),
\]

\[
D_{i1} = \exp \left( \alpha_i^T \tilde{X}_i - e^{\eta_{M1}^T W_i} \sum_{t_{11} \leq Z_i} \lambda_{1l} \right),
\]

\[
D_{i2} = \exp \left( \alpha_i^T \tilde{X}_i \left\{ I(A_i = 0) \exp \left( -e^{\eta_{M2}^T \tilde{X}_i} \sum_{t_{11} \leq Z_i} \lambda_{1l} \right) \right. \right. \\
+ I(A_i = 1) \exp \left( -e^{\eta_{R2}^T \tilde{X}_i} \sum_{t_{3l} \leq Y_i} \lambda_{3l} \right) \right\},
\]

and

\[
D_{i3} = \exp \left( -e^{\eta_{R3}^T W_i} \sum_{t_{3l} \leq Y_i} \lambda_{3l} \right).
\]
In the M-step of the EM algorithm, we maximize the conditional expectation of the complete-data log-likelihood function. In particular, we update $\Lambda_1$, $\Lambda_2$, and $\Lambda_3$ by

\[
\lambda_{1i} = \frac{\sum_{i=1}^{n} \Delta_i^M I(Z_i = t_{1i})}{\sum_{i=1}^{n} (1 - \Delta_i^T + \Delta_i^M \Delta_i^T) I(Z_i \geq t_{1i}) S_{i1}},
\]

\[
\lambda_{2i} = \frac{\sum_{i=1}^{n} \Delta_i^M I(V_i = t_{2i})}{\sum_{i=1}^{n} \Delta_i^M I(V_i \geq t_{2i}) S_{i2}},
\]

\[
\lambda_{3i} = \frac{\sum_{i=1}^{n} (1 - \Delta_i^M) I(Y_i = t_{3i})}{\sum_{i=1}^{n} (1 - \Delta_i^M) I(Y_i \geq t_{3i}) S_{i3}},
\]

where

\[
S_{i1} = \tilde{Pr}(U_i = 1)e^{\eta_{1i}^T W_i} + \tilde{Pr}(U_i = 2)I(A_i = 0)e^{\eta_{2i}^T X_i},
\]

\[
S_{i2} = \tilde{Pr}(U_i = 1)e^{\eta_{1i}^T W_i} + \tilde{Pr}(U_i = 2)I(A_i = 0)e^{\eta_{2i}^T X_i},
\]

\[
S_{i3} = \tilde{Pr}(U_i = 2)I(A_i = 1)e^{\eta_{2i}^T X_i} + \tilde{Pr}(U_i = 3)e^{\eta_{2i}^T W_i}.
\]

We update $\eta_{M1}$ by solving

\[
\sum_{i=1}^{n} \Delta_i^M \left\{ \tilde{Pr}(U_i = 1) W_i - \sum_{j=1}^{n} \frac{I(Z_j \geq Z_i)(1 - \Delta_j^T + \Delta_j^M \Delta_j^T) \tilde{Pr}(U_j = 1)e^{\eta_{1j}^T W_j} W_j}{\sum_{j=1}^{n} I(Z_j \geq Z_i)(1 - \Delta_j^T + \Delta_j^M \Delta_j^T) S_{j1}} \right\} = 0,
\]

and update $\eta_{M2}$ by solving

\[
\sum_{i=1}^{n} \Delta_i^M \left\{ \tilde{Pr}(U_i = 2) I(A_i = 0) \tilde{X}_i - \sum_{j=1}^{n} \frac{I(Z_j \geq Z_i)(1 - \Delta_j^T + \Delta_j^M \Delta_j^T) \tilde{Pr}(U_j = 2) I(A_j = 0)e^{\beta_{M2} + \gamma_{M2} \tilde{X}_j \tilde{X}_j}}{\sum_{j=1}^{n} I(Z_j \geq Z_i)(1 - \Delta_j^T + \Delta_j^M \Delta_j^T) S_{j1}} \right\} = 0.
\]

We update $\eta_{R1}$ by solving

\[
\sum_{i=1}^{n} \Delta_i^M \Delta_i^T \left\{ \tilde{Pr}(U_i = 1) W_i - \sum_{j=1}^{n} \frac{I(R_j \geq V_i) \Delta_j^M \tilde{Pr}(U_j = 1)e^{\eta_{R1}^T W_j} W_j}{\sum_{j=1}^{n} I(R_j \geq V_i) \Delta_j^M S_{j2}} \right\} = 0,
\]

and update $\eta_{R2}$ by solving

\[
\sum_{i=1}^{n} \Delta_i^M \Delta_i^T \left\{ \tilde{Pr}(U_i = 2) I(A_i = 0) \tilde{X}_i \right\} = 0.
\]
 \[- \frac{\sum_{j=1}^{n} I(R_j \geq V_i) \Delta^M_j \hat{\Pr}(U_j = 2) I(A_j = 0) e^{\eta_{r2}^T \tilde{X}_j} \tilde{X}_j}{\sum_{j=1}^{n} I(R_j \geq V_i) \Delta^M_j S_j} \} = 0. \]

We update $\eta_{T2}$ by solving

\[- \frac{\sum_{i=1}^{n} (1 - \Delta^M_i) \Delta^T_i \left\{ \hat{\Pr}(U_i = 2) I(A_i = 1) \tilde{X}_i 
- \sum_{j=1}^{n} I(Y_j \geq Y_i) (1 - \Delta^M_j) \hat{\Pr}(U_j = 2) I(A_j = 1) e^{\eta_{r2}^T \tilde{X}_j} \tilde{X}_j \right\}}{\sum_{i=1}^{n} (1 - \Delta^M_i) S_j} \} = 0, \]

and update $\eta_{T3}$ by solving

\[- \frac{\sum_{i=1}^{n} (1 - \Delta^M_i) \Delta^T_i \left\{ \hat{\Pr}(U_i = 3) W_i 
- \sum_{j=1}^{n} I(Y_j \geq Y_i) (1 - \Delta^M_j) \hat{\Pr}(U_j = 1) e^{\eta_{r3}^T W_j} W_j \right\}}{\sum_{i=1}^{n} (1 - \Delta^M_i) S_j} \} = 0. \]

Finally, we update $\alpha$ by solving

\[- \frac{\sum_{i=1}^{n} \left\{ \hat{\Pr}(U_i = 1) - \exp \left( \alpha_1^T \tilde{X}_i \right) \right\}}{1 + \exp \left( \alpha_1^T \tilde{X}_i \right) + \exp \left( \alpha_2^T \tilde{X}_i \right)} \tilde{X}_i = 0. \]

\[- \frac{\sum_{i=1}^{n} \left\{ \hat{\Pr}(U_i = 2) - \exp \left( \alpha_2^T \tilde{X}_i \right) \right\}}{1 + \exp \left( \alpha_1^T \tilde{X}_i \right) + \exp \left( \alpha_2^T \tilde{X}_i \right)} \tilde{X}_i = 0. \]

Starting with $\theta = 0$ and $\lambda_{kl} = 1/m_k$ for $k = 1, 2, 3$, we iterate between the E-step and the M-step until convergence to obtain the nonparametric maximum likelihood estimators $(\hat{\theta}, \hat{A})$.

**REFERENCES**

Aalen, O. O., Stensrud, M. J., Didelez, V., Daniel, R., Røysland, K., and Strohmaier, S. (2020), “Time-dependent mediators in survival analysis: Modeling direct and indirect effects with the additive hazards model,” *Biometr. J.*, 62, 532–549.
Angrist, J. D., Imbens, G. W., and Rubin, D. B. (1996), “Identification of causal effects using instrumental variables,” *J. Am. Statist. Ass.*, 91, 444–455.

Comment, L., Mealli, F., Haneuse, S., and Zigler, C. (2019), “Survivor average causal effects for continuous time: a principal stratification approach to causal inference with semicompeting risks,” *arXiv preprint arXiv:1902.09304*, .

Copelan, E. A., Biggs, J. C., Thompson, J. M., Crilley, P., Szer, J., Klein, J. P., Kapoor, N., Avalos, B. R., Cunningham, I., and Atkinson, K. (1991), “Treatment for Acute Myelocytic Leukemia with Allogeneic Bone Marrow Transplantation Following Preparation with BuCy2,” *Blood*, 78, 838–843.

Didelez, V. (2019), “Defining causal mediation with a longitudinal mediator and a survival outcome,” *Lifetime Data Anal.*, 25, 593–610.

Fine, J. P., Jiang, H., and Chappell, R. (2001), “On Semi-competing Risks Data,” *Biometrika*, 88, 907–919.

Frangakis, C. E., and Rubin, D. B. (2002), “Principal stratification in causal inference,” *Biometrics*, 58, 21–29.

Huang, Y.-T. (2020), “Causal mediation of semicompeting risks,” *Biometrics*, .

Klein, J. P., and Moeschberger, M. L. (2006), *Survival Analysis: Techniques for Censored and Truncated Data*, New York: Springer.

Lange, T., and Hansen, J. V. (2011), “Direct and Indirect Effects in a Survival Context,” *Epidemiol.*, 22, 575–581.

Lange, T., Vansteelandt, S., and Bekaert, M. (2012), “A Simple Unified Approach for Estimating Natural Direct and Indirect Effects,” *Am. J. Epidemiol.*, 176, 190–195.
Lin, D., Sun, W., and Ying, Z. (1999), “Nonparametric estimation of the gap time distribution for serial events with censored data,” *Biometrika*, 86, 59–70.

Lin, S.-H., Young, J. G., Logan, R., and VanderWeele, T. J. (2017), “Mediation analysis for a survival outcome with time-varying exposures, mediators, and confounders,” *Statistics in medicine*, 36, 4153–4166.

Maller, R. A., and Zhou, S. (1992), “Estimating the proportion of immunes in a censored sample,” *Biometrika*, 79, 731–739.

Mason, M. D., Parulekar, W. R., Sydes, M. R., Brundage, M., Kirkbride, P., Gospodarowicz, M., Cowan, R., Kostashuk, E. C., Anderson, J., Swanson, G. et al. (2015), “Final report of the intergroup randomized study of combined androgen-deprivation therapy plus radiotherapy versus androgen-deprivation therapy alone in locally advanced prostate cancer,” *J. Clin. Oncol.*, 33, 2143–2150.

Tchetgen Tchetgen, E. J. (2011), “On Causal Mediation Analysis with a Survival Outcome,” *Int. J. Biostat.*, 7, 1–38.

VanderWeele, T. J. (2011), “Causal Mediation Analysis with Survival Data,” *Epidemiol.*, 22, 582–585.

Vansteelandt, S., Linder, M., Vandenberghe, S., Steen, J., and Madsen, J. (2019), “Mediation analysis of time-to-event endpoints accounting for repeatedly measured mediators subject to time-varying confounding,” *Statistics in medicine*, 38, 4828–4840.

Wang, W., and Wells, M. T. (1998), “Nonparametric estimation of successive duration times under dependent censoring,” *Biometrika*, 85, 561–572.

Xu, J., Kalbfleisch, J. D., and Tai, B. (2010), “Statistical Analysis of Illness–death Processes and Semicompeting Risks Data,” *Biometrics*, 66, 716–725.
Yu, W., Chen, K., Sobel, M. E., and Ying, Z. (2015), “Semiparametric transformation models for causal inference in time-to-event studies with all-or-nothing compliance,” *J. R. Statist. Soc. B*, 77, 397–415.

Zhang, J. L., and Rubin, D. B. (2003), “Estimation of causal effects via principal stratification when some outcomes are truncated by ‘death’,” *J. Educ. Behav. Stat.*, 28, 353–368.

Zheng, W., and van der Laan, M. (2017), “Longitudinal Mediation Analysis with Time-varying Mediators and Exposures, with Application to Survival Outcomes,” *J. Causal Inference*, 5, 1–24.