Estimation of time-specific intervention effects on continuously distributed time-to-event outcomes by targeted maximum likelihood estimation

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Abstract
This work considers targeted maximum likelihood estimation (TMLE) of treatment effects on absolute risk and survival probabilities in classical time-to-event settings characterized by right-censoring and competing risks. TMLE is a general methodology combining flexible ensemble learning and semiparametric efficiency theory in a two-step procedure for substitution estimation of causal parameters. We specialize and extend the continuous-time TMLE methods for competing risks settings, proposing a targeting algorithm that iteratively updates cause-specific hazards to solve the efficient influence curve equation for the target parameter. As part of the work, we further detail and implement the recently proposed highly adaptive lasso estimator for continuous-time conditional hazards with \( L_1 \)-penalized Poisson regression. The resulting estimation procedure benefits from relying solely on very mild nonparametric restrictions on the statistical model, thus providing a novel tool for machine-learning-based semiparametric causal inference for continuous-time time-to-event data. We apply the methods to a publicly available dataset on follicular cell lymphoma where subjects are followed over time until disease relapse or death without relapse. The data display important time-varying effects that can be captured by the highly adaptive lasso. In our simulations that are designed to imitate the data, we compare our methods to a similar approach based on random survival forests and to the discrete-time TMLE.

Keywords
causal inference, competing risks, nonparametric inference, semiparametric efficiency theory, survival analysis, targeted maximum likelihood estimation

1 | INTRODUCTION

In this work, we consider treatment effect estimation in time-to-event settings where subjects are at risk of failure from one or multiple competing causes (Andersen et al., 1993). In such settings, which often arise in medical research, the effect on the absolute risk probability of a specific cause of interest is a common choice of parameter (Andersen et al., 2017; Ozenne et al., 2020; Scheike & Zhang, 2011). In contrast to hazard ratios obtained from modeling cause-specific hazards, for example, with a Cox regression model (Cox, 1972), the absolute risk probabilities are parameters of the g-computation formula that have a causal interpretation under a set of structural...
assumptions (Gill & Robins, 2001; Hernan & Robins, 2020; Robins, 1986; van der Laan & Robins, 2003). The aim of this work is to provide nonparametric inference for treatment effects on absolute risk (or survival) probabilities in time-to-event settings by specializing and extending the targeted learning (targeted maximum likelihood estimation [TMLE]) methods recently proposed by Rytgaard et al. (2022). The setting considered by Rytgaard et al. (2022) is both more and less general than the one we consider; whereas we restrict ourselves to the “classical” time-to-event setting, with only baseline covariates and baseline treatment decision, we extend the setting of Rytgaard et al. (2022) by allowing for competing risk events. As a motivating example, we consider a publicly available dataset on follicular cell lymphoma where subjects are followed over time until disease relapse or death without relapse. Based on these data, we wish to measure the effect of chemotherapy/radiation treatment at baseline, adjusted for pretreatment covariates. As previously found (see, e.g., Scheike & Zhang, 2011), these data involve nonproportional hazards that require flexible nuisance parameter estimation.

Estimation of average treatment effects on absolute risk probabilities could be carried out, for example, by use of Cox regression models (Cox, 1972) to model causespecific hazards, or by the Fine and Gray method (Fine & Gray, 1999) to model subdistribution hazard functions. However, both methods are limited by the assumption of proportional hazards, either on the cause-specific or the subdistribution hazard scale, and the requirement to correctly specify main effects and interactions between treatment and confounders. In recent years, semiparametric efficient and doubly robust estimators incorporating the efficient influence function (Bickel et al., 1993; Tsiatis, 2007; van der Vaart, 2000; van der Laan & Robins, 2003) such as estimation equation methodology (Hubbard et al., 2000; Robins & Rotnitzky, 1992; van der Laan & Robins, 2003) and TMLE, have gained great popularity in many fields and are increasingly used to draw inference about treatment effects. In contrast to the weighted estimation equation methods, TMLE works by updating an estimator for (relevant parts of) the data-generating distribution to construct semiparametrically efficient substitution estimators. TMLE has further been successfully coupled with data-adaptive modeling techniques through loss-based cross-validated selection (van der Laan et al., 2007) and nonparametric highly adaptive lasso estimation (van der Laan, 2017). This enables valid inference under only very mild nonparametric assumptions on the data-generating mechanism, avoiding usual limitations of traditional parametric methods.

Generally, TMLE proceeds in two steps. Initial estimators are constructed for the nuisance parameters in the first step that is then followed by a targeting step that reduces bias for the causal effect, improves precision, and ensures reliable statistical inference in terms of confidence intervals and $p$-values. Although algorithms to carry out the targeting step have been extensively developed for treatment effect estimation in survival analysis settings when events are observed on a discrete time scale (Benkeser et al., 2018; Cai & van der Laan, 2019; Moore & van der Laan, 2009a, 2009b, 2009c; Stitelman et al., 2011; Stitelman & van der Laan, 2011; van der Laan & Gruber, 2012), these methods require artificial discretization to be applied to events observed in continuous, or very fine discrete, time (Sofrygin et al., 2019), likely leading to bias and waste of information (Ferreira Guerra et al., 2020). Even in our setting with only baseline confounding and treatment interventions, our simulation study demonstrates the insufficiency of the existing discrete-time survival TMLE as well as its dependence on the choice of discretization scheme employed. To generalize the targeting procedure proposed in Section 5.2 of Rytgaard et al. (2022) for competing risks settings, we propose to iteratively carry out targeted maximum likelihood update steps along submodels through current estimators for the cause-specific hazards. We also refer the interested reader to the paper Rytgaard and van der Laan (2022), reviewing our targeting procedure proposed here in a simplified setting with offset in the Cox model.

As part of the present work, we detail and implement the highly adaptive lasso estimator for continuous-time baseline covariate-dependent hazards (see Rytgaard et al., 2022, Appendix B) based on Poisson regression modeling techniques (Andersen et al., 1993; Lindsey, 1995). We emphasize that not many machine learning methods exist that are applicable in continuous time-to-event data settings, so that this highly adaptive lasso fills an important gap. In addition, the highly adaptive lasso estimator has been proven to achieve proper convergence rates required for asymptotically linear and efficient target parameter estimation (Bibaut & van der Laan, 2019; van der Laan, 2017) under very mild nonparametric assumptions on the data-generating mechanism (van der Laan, 2017). In contrast, other flexible methods, such as kernel estimators, usually require strong smoothness assumptions and even under such assumptions commonly suffer from the curse of dimensionality. In our simulation study, we demonstrate the desirable properties of the highly adaptive lasso and make comparisons to usage of random survival forests (Ishwaran et al., 2008) for which the needed rate of convergence results has not been established.

In the Supporting Information, we derive exact expressions for efficient influence functions and second-order remainders. We further establish double robustness properties of the considered survival and competing risks
estimation problems and show that $n^{-1/4}$ convergence is enough to establish asymptotic linearity and efficiency of the targeted maximum likelihood estimator for the intervention-specific absolute risk probability.

1.1 Organization of paper

Our paper is organized as follows. In Section 2, we introduce the setting and notation of the considered time-to-event setting. In Section 2.1, we define our statistical target parameter with a causal interpretation under the usual assumptions of consistency, no unmeasured confounding, and positivity. In Section 3, we give an overview of the construction of our targeted substitution estimator and summarize its theoretical properties. In Section 4, we describe our targeting algorithm to solve the efficient influence curve equation. In Section 5, we detail the nonparametric highly adaptive lasso estimator for continuous-time conditional hazards. In Section 6, we present our simulation study. In Section 7, we use our methods to analyze the dataset on follicular cell lymphoma. We close with a discussion in Section 8.

2 SETTING AND NOTATION

We consider throughout unit-specific observed data on the form $O = (L, A, T, \Delta)$, containing a vector of information on pretreatment characteristics ($L \in L \subseteq \mathbb{R}^d$), information on what treatment the unit was exposed to ($A \in A = \{0, 1\}$), how long the unit was under observation ($T \in \mathbb{R}_+$), what event of interest was observed for the unit ($\Delta \in \{1, \ldots, J\}$), or if the unit was censored ($\Delta = 0$). We introduce the variables $T \in \mathbb{R}_+$ and $C \in \mathbb{R}_+$ as the times to event and censoring, respectively, such that the observed time is $\hat{T} = \min(T, C)$ and the event indicator can be written $\Delta = 1[\hat{T} \leq C]\Delta$ with $\Delta \in \{1, \ldots, J\}$. Our data consist of a sample $\{O_{ij}^n\}_{i=1}^n$ of independent and identically distributed observations of $O \sim P_0$, where $P_0$ is the distribution of the observed data with density $p_0$ given by

$$p_0(o) = \mu_0(\ell)\pi_0(a \mid \ell) \prod_{j=1}^J (\lambda_{0,j}(t \mid a, \ell))^{I[\Delta=j]} \mathbb{P}_0,$$

$$o = (\ell, a, t, \delta).$$

We assume that $P_0$ belongs to a statistical model $M$. In the display above, $\mu_0$ denotes the density of $L$ with respect to an appropriate dominating measure $\nu$. $\pi_0(\cdot \mid L)$ is the conditional distribution of $A$ given $L$, $\lambda_{0,j}(t \mid a, \ell) = \lim_{h \to 0} h^{-1} P_0(T \leq t + h, \hat{\Delta} = j \mid T \geq t, A = a, L = \ell)$ denotes the cause $j$ specific hazard,

$$\lambda_0(t \mid a, \ell) = \lim_{h \to 0} h^{-1} P_0(C \leq t + h \mid C \geq t, A = a, L = \ell),$$

denotes the hazard for the distribution of the censoring time $C$, and $S_0(t \mid a, \ell) = \exp[- \int_0^t \sum_{j=1}^J \lambda_{0,j}(s \mid a, \ell)ds]$ and $S_0^*(t \mid a, \ell) = \exp[- \int_0^t \lambda_{0,j}(s \mid a, \ell)ds]$ denote the survival functions for $T$ and $C$, respectively. Note that the factorization in (1) relies on coarsening at random (van der Laan & Robins, 2003), which we will assume throughout: this entails that the censoring mechanism at any time only depends on the observed history up till that time.

2.1 Target of estimation

We are interested in estimation of the target parameter $\Psi_{\ell}^{\text{int}} : M \to \mathbb{R}$ defined as the intervention-specific absolute risk beyond time $\tau$:

$$\Psi_{\ell}^{\text{int}}(P) = \int_{\ell} \sum_{a=0,1} \int_{\Delta=\{1,\ldots,J\}} F_1(\tau \mid a, \ell) \pi^{\text{int}}(a \mid \ell) \mu(\ell) d\nu(\ell)$$

$$= \mathbb{E}_{\pi^{\text{int}}}[T \leq \tau, \Delta = 1],$$

where $F_1(t \mid a, \ell) = \int_0^t S(s \mid a, \ell) \lambda_1(ds \mid a, \ell)$ is the absolute risk function for the event of interest ($j = 1$) (Gray, 1988) and $\pi^{\text{int}}$ is a distribution governing a hypothetical treatment decision at baseline. To define the average treatment effect, for example, we substitute for $a' = 0, 1$ the interventional $\pi^{\text{int}}(a \mid \ell) = \mathbb{I}(a = a')$ for $\pi^{\text{int}}$ in (2), where $\pi^{\text{int}}$ is a degenerate distribution that puts all mass in $A = a'$. In the Supporting Information, we detail how (2) arises under interventions on the data-generating distribution (specializing the setting of Rygaard et al., 2022), imposing the treatment distribution $\pi^{\text{int}}$ at baseline and no censoring during the follow-up period. Here, we also review the proof that assumptions of consistency, no unmeasured confounding, and positivity yield the causal interpretation of the target parameter (2) as the risk we would observe had subjects been treated according to the treatment strategy $\pi^{\text{int}}$. We denote by $\psi_0 = \Psi_{\ell}^{\text{int}}(P_0)$ the true value of the target parameter.

3 TARGETED SUBSTITUTION ESTIMATION

In the following sections, we describe our estimation procedure to construct a targeted substitution estimator $\hat{\psi}_n^* = \Psi_{\ell}^{\text{int}}(\hat{P}_n)$ for the target parameter. This procedure consists of the two steps:

STEP 1: Construction of nonparametric estimators $\hat{\lambda}_{1,n}, \ldots, \hat{\lambda}_{J,n}, \hat{\lambda}_{\ell,n}$, and $\hat{\pi}_n$ via highly adaptive lasso
estimation for the conditional cause-specific hazards, the hazard of the censoring distribution and for the distribution of treatment (Section 5).

**Step 2:** A targeting algorithm to obtain updated estimators \( \hat{\lambda}_1, \ldots, \hat{\lambda}_j, \) from the initial estimators \( \hat{\lambda}_1, \ldots, \hat{\lambda}_j \) for the conditional cause-specific hazards (Section 4).

We refer to \( \pi, \lambda, \) and \( \lambda_1, \ldots, \lambda_j \) as the nuisance parameters for our estimation problem and note that \( \hat{\beta}_n \) consists of the estimators \( \hat{\lambda}_1, \ldots, \hat{\lambda}_j \) obtained from Steps 1 and 2 and the estimators \( \hat{\lambda}_c, \hat{\pi} \) obtained from Step 1. We obtain the average over the distribution of covariates (with density \( \mu \)) simply as the empirical average over the observed data. Thus, our final estimator for the target parameter is obtained as

\[
\hat{\psi}_n = \Psi_\pi^\text{int}(\hat{P}_n) = \frac{1}{n} \sum_{i=1}^n \left( \sum_{a=0,1} \int_0^\tau \exp \left( - \int_0^\tau \sum_{j=1}^n \hat{\lambda}_{j,a}(t | a, \nu) \frac{d \pi_{\nu}(a | \nu)}{\pi(a | \nu)} \right) \right) \cdot (3)
\]

### 3.1 Efficient influence function

The estimator defined by (3) after carrying out Step 1 and Step 2 achieves desirable asymptotic properties under very mild assumptions on the statistical model \( \mathcal{M} \) (see Sections 3.2 and 3.3). In Section 4, we present our targeting algorithm for Step 2 and in Section 5, we present the highly adaptive lasso estimator for Step 1. Here, we present notation for the efficient influence function.

We let \( D_\tau^\text{int} \) denote the efficient influence function (Bickel et al., 1993; van der Vaart, 2000) for the target parameter \( \Psi_\pi^\text{int} : \mathcal{M} \to \mathbb{R} \) and the nonparametric model \( \mathcal{M} \). Note that this efficient influence function is well known from the literature (Moore & van der Laan, 2009a, 2009b; Robins & Rotnitzky, 1992; van der Laan & Robins, 2003; van der Laan & Rose, 2011). It can be written in the form

\[
D_\tau^\text{int}(P)(\lambda_1, \ldots, \lambda_j, \lambda_c, \pi)(A, L)
\]

\[
= \frac{1}{n} \sum_{i=1}^n \int_0^\tau w_{\tau, j, a}(\lambda_1, \ldots, \lambda_j, \lambda_c, \pi)(A, L) \left( N_j(dt) - \mathbb{I}[T \geq \tau] \right) \right) + F_1(\tau | a, L) - \Psi_\pi^\text{int}(P),
\]

(4)

where \( N_j(t) = \mathbb{I}[T \leq t, \Delta = j] \) denotes the observed counting process (Andersen et al., 1993) for events of type \( j \) and where the functions \( w_{\tau, j, a} \) are defined as

\[
w_{\tau, j, a}(\lambda_1, \ldots, \lambda_j, \lambda_c, \pi)(A, L)
\]

\[
= \frac{\pi_{\nu}(a | \nu)}{\pi(a | \nu)} \frac{1}{S(t | \nu)} \left( \frac{F_1(t | a, L) - F_0(t | a, L)}{S(t | a, L)} \right),
\]

for \( j = 1 \),

\[
w_{\tau, j, a}(\lambda_1, \ldots, \lambda_j, \lambda_c, \pi)(A, L)
\]

\[
= \frac{\pi_{\nu}(a | \nu)}{\pi(a | \nu)} \frac{1}{S(t | \nu)} \left( \frac{F_1(t | a, L) - F_0(t | a, L)}{S(t | a, L)} \right),
\]

for \( j \neq 1 \).

The derivation of the efficient influence function can be found in the Supporting Information. As we will see in Section 4, Step 2 of our estimation procedure is constructed such that the estimator \( \hat{P}_n^* \) consisting of estimators \( \hat{\lambda}_c, \hat{\pi} \) and \( \hat{\pi}_n \) obtained from Step 1 and Step 2 solves

\[
P_n D_\tau^\text{int}(\hat{P}_n) = o_p(n^{-1/2}),
\]

(6)

referred to throughout as the efficient influence curve equation. Note that \( o_p(1) \) denotes a term that converges to zero in probability, \( o_p(n^{-1/2}) \) a term that when multiplied by \( n^{1/2} \) converges to zero in probability, and \( P_n \) denotes the empirical distribution of the data \{\text{O} \}_{i=1}^{\text{N}}.

### 3.2 Assumptions needed for asymptotic linearity and efficiency

Throughout we make the following assumptions on the statistical model \( \mathcal{M} \):

**Assumption 1.** For any \( P \in \mathcal{M} \), we assume that the nuisance parameters \( \lambda_1, \ldots, \lambda_j, \lambda_c \) and \( \pi \) can be parameterized by functions with finite sectional variation norm that are càdlàg (i.e., right continuous with left limits) in \((t, A, L)\) and \( L \), respectively, on a bounded support for \( L \).

**Assumption 2.** We assume that positivity holds in the sense that \( S^c(\tau | a, L) \pi(a | L) > \eta > 0 \), a.e., for \( a = 0,1 \), and that \( S(\tau | A, L) > \eta' > 0 \), a.e.

We remark that the space of càdlàg functions with finite sectional variation norm does not include wild functions with unbounded variation (an example could be cos(1/x), or a Brownian motion), but otherwise is a very mild constraint allowing for discontinuities and nondifferentiability.

### 3.3 Asymptotic properties of the targeted substitution estimator

Here, we clarify the asymptotic properties of the targeted estimator \( \hat{\psi}_n = \Psi_\pi^\text{int}(\hat{P}_n^*) \) achieved with our estimation procedure, relying solely on nonparametric assumptions on the statistical model \( \mathcal{M} \) stated in Section 3.2. Particularly, Theorem 1 below yields the asymptotic properties
of the estimator for the target parameter achieved with our estimation procedure. The proof can be found in the Supporting Information.

**Theorem 1** (Asymptotic properties of the targeted substitution estimator). Under Assumptions 1 and 2, the targeted substitution estimator \( \hat{\psi}_n = \Psi_{\hat{\epsilon}}(\hat{P}_n) \) admits the representation

\[
\sqrt{n}(\hat{\psi}_n - \psi_0) = \sqrt{n}P_nD_{\hat{\epsilon}}(P_0) + o_P(1),
\]

that is, \( \hat{\psi}_n \) is asymptotically linear with influence function equal to the efficient influence function.

Note that a straightforward consequence of Theorem 1 is that we can use the asymptotic normal distribution \( \sqrt{n}(\hat{\psi}_n - \psi_0) \xrightarrow{D} \mathcal{N}(0, P_0D_{\hat{\epsilon}}(P_0)) \) following from (7) to provide an approximate two-sided confidence interval. The asymptotic variance of the estimator is given from the variance of the efficient influence function and can be estimated by \( \hat{\sigma}_n^2 = P_n(D_{\hat{\epsilon}}(\hat{P}_n))^2 \).

### 4 | TARGETING ALGORITHM

The goal of the targeting algorithm is to obtain updated estimators \( \hat{\lambda}_{1,n}, \ldots, \hat{\lambda}_{J,n} \) for the conditional cause-specific hazards, given the initial estimators \( \hat{\lambda}_{1,n}, \ldots, \hat{\lambda}_{J,n}, \hat{\pi}_n \) and \( \hat{\lambda}_c \) from Step 1 of the estimation procedure from Section 3, such that \( \hat{P}_n \) consisting of estimators \( \hat{\lambda}_{1,n}, \ldots, \hat{\lambda}_{J,n}, \hat{\pi}_n \) solves the efficient influence curve equation (6). Since any substitution estimator on the form (3), with \( \mu \) estimated by the empirical distribution of \( L \) already solves the two last terms of the efficient influence curve equation, only the first terms of (4) remain to establish (6). Here, we describe how to achieve this, supposing for now we have at hand the initial estimators.

Overall, our targeting algorithm is formed by iterative update steps for \( \hat{\lambda}_{1,n}, \ldots, \hat{\lambda}_{J,n} \) defining a sequence of estimators,

\[
\hat{\lambda}_{j,n} = \hat{\lambda}_{j,n,k=0}, \hat{\lambda}_{j,n,k=1}, \ldots, \hat{\lambda}_{j,n,k=k^*},
\]

for \( j = 1, \ldots, J \). The update step for each element \( \hat{\lambda}_{j,n,k} \) of the sequence of estimators (8) is performed along a one-dimensional fluctuation model through \( \hat{\lambda}_{j,n,k}, \) where the fluctuation model is chosen such that its score equals a relevant term of the efficient influence function. For each cause-specific hazard \( \hat{\lambda}_j \), we define particularly the multiplicative hazards-type fluctuation model through \( \hat{\lambda}_j \) at \( \varepsilon_j = 0 \)

\[
\lambda_j^{\epsilon_j}(t \mid A, L) = \lambda_j(t \mid A, L)\exp(\varepsilon_jw_{j,t}^{\text{int}}(\lambda_j, \ldots, \lambda_j, \lambda^c, \pi)(A, L)), \quad \varepsilon_j \in \mathbb{R},
\]

with fluctuation parameter \( \varepsilon_j \in \mathbb{R} \) and with the functions \( w_{j,t}^{\text{int}} \) defined by (5). With \( (O, \lambda) \rightarrow \epsilon \loglik(\lambda)(O) \) denoting the log-likelihood function for \( \lambda_j \),

\[
\epsilon_{\loglik}(\lambda)(O) = \int_0^\tau \log \lambda_j(t \mid A, L)N_j(dt)
\]

\[- \int_0^\tau \{T \geq t\}w_{j,t}^{\text{int}}(\lambda_1, \ldots, \lambda_j, \lambda^c, \pi)(A, L)\lambda_j(t \mid A, L)dt,
\]

we have the property that

\[
\frac{d}{d\varepsilon}\bigg|_{\varepsilon=0} \epsilon_{\loglik}(\lambda)(O) = \int_0^\tau w_{j,t}^{\text{int}}(\lambda_1, \ldots, \lambda_j, \lambda^c, \pi)(A, L)N_j(dt)[-0.5\epsilon] - \int_0^\tau \{T \geq t\}w_{j,t}^{\text{int}}(\lambda_1, \ldots, \lambda_j, \lambda^c, \pi)(A, L)\lambda_j(t \mid A, L)dt,
\]

recognizing the right-hand side as the \( j \)th term of the efficient influence curve equation. The maximum likelihood estimator for the fluctuation parameter \( \hat{\epsilon}_{j,k} = \arg\max P_n\epsilon_{\loglik}(\hat{\lambda}_{j,n,k}) \) along the fluctuation model evaluated in the current estimators \( \hat{\lambda}_{1,n,k}, \ldots, \hat{\lambda}_{J,n,k} \) now defines an updated estimator \( \hat{\lambda}_{j,n,k+1}(t \mid A, L) := \hat{\lambda}_{j,n,k}(t \mid A, L)\exp(\hat{\epsilon}_{j,k}w_{j,t}^{\text{int}}(\lambda_{1,n,k}, \ldots, \lambda_{J,n,k}, \hat{\lambda}_c, \hat{\pi}_n)(A, L)) \), for \( j = 1, \ldots, J \). This constitutes the targeting iteration from \( k \) to \( k+1 \), corresponding to updating \( \hat{\lambda}_{j,n,k} \) into \( \hat{\lambda}_{j,n,k+1} \). In each step, we achieve, per construction, that \( \frac{d}{d\varepsilon}\bigg|_{\varepsilon=0} P_n\epsilon_{\loglik}(\hat{\lambda}_{j,n,k+1}) = 0 \). The process is carried out iteratively for \( k = 0, 1, \ldots \), and the steps from \( k \) to \( k+1 \) are repeated until \( \hat{\epsilon}_{j,k+1} = 0 \) at which point

\[
\frac{d}{d\varepsilon}\bigg|_{\varepsilon=0} P_n\epsilon_{\loglik}(\hat{\lambda}_{j,n,k+2}) = 0.
\]

As by (11), the score of the fluctuation model evaluated at zero equals the \( j \)th term of the efficient influence curve, so that the estimator \( \hat{\lambda}_{j,n} = \hat{\lambda}_{j,n,k+1} \) together with \( w_{j,t}^{\text{int}}(\lambda_{1,n,k}, \ldots, \lambda_{J,n,k}, \hat{\lambda}_c, \hat{\pi}_n) \) solves the \( j \)th term of the efficient influence curve equation. Thus, the estimator \( \hat{P}_n \) consisting of \( \hat{\lambda}_c, \hat{\pi}_n \), and \( \hat{\lambda}_{1,n}, \ldots, \hat{\lambda}_{J,n} \) solves all terms of the efficient influence curve equation. In practice, we stop the iterations when \( |P_nD_{\hat{\epsilon}}(\hat{P}_n)| \leq s_n \) for a stopping criterion \( s_n \) such that \( s_n = \varphi(n^{-1/2}) \). As long as the likelihood is bounded along the fluctuation model iteratively defined in each current estimator, we can for any choice \( s_n \) always proceed iterations far enough such that this holds. We can, for example, use \( s_n = \sqrt{P_n(D_{\hat{\epsilon}}(\hat{P}_n))^2/(n^{-1/2} \log n)} \), where \( P_n(D_{\hat{\epsilon}}(\hat{P}_n))^2 \) estimates the variance of the efficient
influence function and ̂Pn consists of the estimators ̂λ1,n,..., ̂λc,n and ̂πn obtained from Step 1 of the estimation procedure.

5 | NONPARAMETRIC HIGHLY ADAPTIVE LASSO ESTIMATION OF THE CONDITIONAL HAZARD

To carry out our targeting algorithm, we need initial estimators for the conditional hazard ̂λ | Z of the censoring distribution, for the conditional cause-specific hazards ̂λ1,..., ̂λc and for ̂π the conditional distribution of treatment given covariates. For the conditional hazards, we can apply the highly adaptive lasso estimator that we describe here. For the conditional distribution of treatment, highly adaptive lasso estimation has already been developed and implemented (alternatively, this could be estimated with any binary regression method, including logistic regression and a large variety of machine learning algorithms).

The highly adaptive lasso estimator for continuous-time hazards was previously described for a more general setting by Rytgaard et al. (2022). Here, we detail it for our setting where we generally need estimation of ̂λ( | Z) for baseline information Z, which, for our purposes, consists of the baseline treatment and covariates, Z = (A,L) ∈ ℝd+1. Note that λ could be the censoring hazard ̂λc or any of the cause-specific hazards ̂λ1,..., ̂λc. We consider the reparameterization as follows:

\[
\lambda_f(t | Z) = \exp(f(t,Z)), \quad f : [0, \tau] \times \mathbb{R}^{d+1} \rightarrow \mathbb{R}.
\]

(12)

We let 𝒪 denote the class of càdlàg functions with sectional variation norm (Gill et al., 1995; van der Laan, 2017) bounded by a constant ̄M < ∞. Throughout, we make the assumption that f ∈ 𝒪3 by which it follows that Assumption 1 as stated in Section 3.2 is fulfilled.

For the following, we let (O,f) → 𝒥(f)(O) denote the log-likelihood loss function, that is, 𝒥(f)(O) = −loglik(̂λ)(O) with (O, ̂λ) → ̂λloglik(λ)(O) from Equation (10). In its practical construction, the highly adaptive lasso estimator is defined as the minimizer of Pn,̂J(f) over discrete functions f ∈ 𝒪. We describe representations of such discrete functions in Section 5.1, after which we define the minimization problem yielding the highly adaptive lasso estimator in Section 5.2. As detailed by previous work (see, e.g., Rytgaard et al., 2022, Appendix B.1.1), the nice form of these representations arise from the fact that f ∈ 𝒪 yields a representation for f in terms of its measures over sections (Gill et al., 1995), which for functions over a discrete support becomes a finite linear combination of indicator functions over support points (van der Laan, 2017). Since all finite functions in 𝒪 admit such representations, the highly adaptive lasso minimization problem becomes an L₁-penalized regression problem with coefficients representing the pointmass assigned to support points.

5.1 | Notation for basis function representation

The formal definition of the highly adaptive lasso estimator requires a fair amount of notation that we introduce here. Note that we specialize this notation for a simplified example further below in this section. For all that follows, [x₁,x₂] ⊂ ℝd+1 denotes the support of z → f(t,z).

For a subset of indices S ⊂ {1,..., d + 1}, we denote by zS the S-specific coordinates of z ∈ ℝd+1 and by ∑₁≤r≤d+1 \( \sum_{S \subseteq \{1, \ldots, d+1\}} \) the sum of all subsets of S ⊂ {1,..., d + 1}. We define by z ↦ f₁,S(t,z) = f(t,z₁,...,z₁,S) the (t, S)-specific section of f that only varies along the time axis and the coordinates in S, by z ↦ fₛ(z) = f(0,z₁,...,z₁,S) the S-specific section of f that only varies along the coordinates in S, and lastly by t → f₁(t) = f(t,x₁) the t-specific section of f that only varies along the time axis.

We consider a grid of time points partitioning [0, τ], 0 = t₀ < t₁ < ... < tₖ < tₖ₊₁ = τ, as well as a partitioning cupdot_{m∈I} Z_m = [x₁,x₂] of the sample space of Z into (d + 1)-dimensional cubes with indices in the set I. We let zₘ ∈ Zₘ denote the midpoint of the cube Zₘ with the corresponding S-specific coordinates zₘ,S. We further let Iₘ denote the index set for the subset S, noting that Iₘ₁ ⊆ Iₘ₂ for S₁ ⊆ S₂.

We now introduce the indicator basis functions ϕₘ(t) = 1{t ≤ t} and ϕₘₙₖ(z) = 1{zₘ,S ≤ z₁ ≤ zₙ,S} and consider the discrete approximation fₘ of f with support over these points admitting a representation as follows:

\[
f_m(t,z) = \sum_{r=0}^{K} \phi_r(t)\beta_r + \sum_{r=0}^{K} \sum_{S \subseteq \{1, \ldots, d+1\}} \sum_{m \in I(S)} \phi_r(t)\phi_{S,S}(z)\beta_{r,S,m}.
\]

(13)

In the display above, the β coefficients represent pointmasses assigned by fₘ. Particularly, we have (with Δ f(v) = f(v) − f(v−)) that:

- \( \beta_{r,S,m} = \Delta f_{[,1,S}(t_r,z_{m,S}) \) denotes the pointmass that the S-specific section of fₘ assigns to the point defined by zₘ and t_r;
- \( \beta_r = \Delta f_{[,1}(t_r) \) denotes the increments along the time axis alone;
\[ \beta_{0,s,m} = \triangle f_{\beta,s}(z_{m,s}) \] denotes the pointmass that the 
S-specific section of \( f_\beta \) assigns along the z-axis alone;
\[ \beta_0 = f_{\beta}(0, x_i) \] is the pointmass assigned by \( f_\beta \) to left end of 
the support.

Consider, for example, the much simplified setting 
with only a single (continuous) baseline covariate \( L \in \{x_{L,1}, x_{L,2}\} \). In this case, we have that \( \{x_{1}, x_2\} = \{0, 1\} \times \{x_{L,1}, x_{L,2}\} \) and the possible subsets of indices are \( S \in \{\{1\}, \{2\}, \{1, 2\}\} \) with \( I(S_1) = 1 \) and \( I(S_2) = I(S_3) = I_L \) 
contains the indices counting the number of distinct values of 
a grid \( \{\ell_1, \ldots, \ell_{L_1}\} \) chosen for \( L \). The basis representation 
in (13) with the partitioning defined by \( 0 = t_0 < t_1 < \cdots < 
\tau < \tau_{R+1} = \tau \) for the time axis and the values \( \{\ell_1, \ldots, \ell_{L_1}\} \) 
for the covariate axis then becomes:

\[
\begin{align*}
\hat{f}_{\beta}(t,a,\ell) &= \sum_{r=0}^{R} \sum_{m \in \mathcal{I}_L} 1\{t_r \leq t\} 1\{\ell \leq \ell_m\} \beta_{r,A} \\
&+ \sum_{r=0}^{R} \sum_{m \in \mathcal{I}_L} 1\{t_r \leq t\} 1\{\ell \leq \ell_m\} \beta_{r,L} \\
&+ \sum_{r=0}^{R} \sum_{m \in \mathcal{I}_L} 1\{t_r \leq t\} 1\{a \leq a\} 1\{\ell \leq \ell_m\} \beta_{r,A,L}.
\end{align*}
\]

Generally, we refer to the stacked vector of \( \beta_{r}, \beta_{r,L}, \beta_{r,A,L} \) 
as the vector of parameter coefficients and note that this vector completely 
characterizes the behavior of \( f_{\beta} \). The sectional variation norm (Gill et al., 1995; 
vander Laan, 2017) of \( f_{\beta} \) becomes a sum over the 
absolute values of its coefficients, \( \|f_{\beta}\|_1 = \sum_{r=0}^{R} |\beta_r| + 
\sum_{r=0}^{R} \sum_{m \in \mathcal{I}(S)} |\beta_{r,s,m}| = \|\beta\|_1 \), that is, the 
 sectional variation norm of \( f_{\beta} \) equals the \( L_1 \)-norm of the 
coefficient vector.

\subsection{The highly adaptive lasso estimator}

We can now define the highly adaptive lasso estimator as follows.

**Definition 1** (Highly adaptive lasso estimator). The highly 
adaptive lasso estimator for \( f \) is obtained as \( \hat{f}_n = f_{\beta_n} \) 
where:

\[
\hat{f}_n = \text{argmin}_{\beta} \mathbb{P}_n \mathcal{L}(f_{\beta}), \quad \text{s.t., } \|\beta\|_1 \leq M. \tag{14}
\]

Notably, (14) corresponds to an \( L_1 \)-penalized regression 
with the indicator functions \( \phi_{\ell}(t) \) and \( \phi_{a}(t) \phi_{s,m}(z) \) 
as covariates and \( \beta_{r}, \beta_{r,L}, \beta_{r,A,L} \) as the corresponding coefficients.

We show in the Supporting Information that, when 
choosing the support of \( f_{\beta} \) fine enough, the \( L_1 \)-norm of 
the coefficient vector approximates the sectional variation 
norm of \( f \) and the solution \( f_{\beta} \) to the minimization 
problem defined by (14) in Definition 1 approximates the 
infinite-dimensional minimization problem of minimizing 
\( \mathbb{P}_n \mathcal{L}(f) \) over all \( f \in \mathcal{F}_\beta \).

One way to solve the minimization problem in (14) 
in practice (see the Supporting Information) is by stan-
dard \( L_1 \)-penalized Poisson regression software, exploiting 
the correspondence between the log-likelihood defined by 
(10) and the Poisson log-likelihood (Andersen et al., 1993; 
Lindsey, 1995). The highly adaptive lasso estimator \( \hat{f}_n \) 
can next be plugged into (12), providing an estimator 
for the hazard itself. Cross-validation based on the 
log-likelihood loss can then be used to data-adaptively 
select the bound on the variation norm: by the oracle 
properties of cross-validation (van der Laan & Dudoit, 
2003; van der Vaart et al., 2006), we only need at least 
one of the candidates to be larger than the true variation 
norm.

\section{Summary of theoretical results for 
the highly adaptive lasso estimator}

We here provide a summary of the theoretical results for 
the highly adaptive lasso estimator. These results rely on 
the double robust structure of the so-called second-order 
remainder (see below) as well as the sufficiently fast con-
vergence rate of the highly adaptive lasso estimator. The 
asymptotic negligibility of this second-order remainder, as 
established by Lemma 1 below, is a crucial ingredient in 
the proof of Theorem 1. It is a result that usually requires much 
more restrictive assumptions than the ones we need, and it 
has not been established, for example, for the random sur-
vival forests that we compare the highly adaptive lasso to 
in our simulation study.

We here define the second-order remainder for \( P \in \mathcal{M} \) 
by

\[
R(P, P_0) := \Psi_{\tau}^{\text{int}}(P) - \Psi_{\tau}^{\text{int}}(P_0) + P_0 D_{\tau}^{\text{int}}(P), \tag{15}
\]

which, as we show in the Supporting Information, can be 
written out explicitly as

\[
R(P, P_0) = \Psi_{\tau}^{\text{int}}(P) - \Psi_{\tau}^{\text{int}}(P_0)
+ P_0 D_{\tau}^{\text{int}}(P) = \int_{\ell} \sum_{a=0}^{1} \int_{a}^{\tau} S_0(s- \mid a, \ell) 
\left( \frac{\pi_0(a \mid \ell) S_0(s- \mid a, \ell)}{\pi(a \mid \ell) S(s- \mid a, \ell)} - 1 \right) \left( 1 - \frac{F_{\ell}(s- \mid a, \ell) - F_{\ell}(s \mid a, \ell)}{S(s \mid a, \ell)} \right). \]
\[ (\Lambda_0(ds \mid a, \ell) - \Lambda_1(ds \mid a, \ell)) \mu^{\text{int}}(a \mid \ell) d\nu(\ell) \\
- \sum_{j=1}^J \int \sum_{a=0,1} \int_{0}^{\tau} S_0(s \mid a, \ell) \left( \frac{\pi_0(a \mid \ell) S_0(s \mid a, \ell)}{\pi(a \mid \ell) S(s \mid a, \ell)} - 1 \right) \\
\left( F_1(\tau \mid a, \ell) - F_2(\tau \mid a, \ell) \right) \left( -0.3 cm \right) (\Lambda_0(ds \mid a, \ell) - \Lambda_1(ds \mid a, \ell)) \mu^{\text{int}}(a \mid \ell) d\nu(\ell) \].

We say that this second-order remainder displays a double robustness structure, noting that \( R(P, P_0) = 0 \) if either \( \pi_0(a \mid \ell) = \pi(a \mid \ell) \) and \( S_0(t \mid a, \ell) = S(t \mid a, \ell) \) for all \( t \in (0, \tau) \), or if \( \lambda_0(t \mid a, \ell) = \lambda(t \mid a, \ell) \) for all \( t \in (0, \tau] \) and \( j = 1, \ldots, J \). This implies particularly the well-known benefits that consistent estimation requires only providing consistent estimators for either the censoring distribution and the treatment distribution or the cause-specific hazards for all competing risks. It further yields the following result on asymptotic negligibility of the second-order remainder achieved with the highly adaptive lasso. Ultimately, this is what we need to obtain asymptotic linearity of the resulting targeted estimator.

**Lemma 1** (Asymptotic negligibility of the second-order remainder). Let \( G(t \mid a, \ell) := S'(t \mid a, \ell) \pi(a \mid \ell) \). The double robust structure implies that \( R(P_0^n, P_0) = o_P(n^{-1/2}) \) is achieved when both \( G_0 \) and \( \lambda_0 \) are estimated at a rate faster than \( o_P(n^{-1/4}) \) with respect to the \( L_2(\pi^{\text{int}} \otimes \mu_0 \otimes \rho) \)-norm where \( \|f\|_{\pi^{\text{int}} \otimes \mu_0 \otimes \rho} = \sqrt{\int f^2 d(\pi^{\text{int}} \otimes \mu_0 \otimes \rho)} \) and \( \rho \) denotes the highly adaptive lasso estimator.

The proof of Lemma 1 can be found in the Supporting Information.

### 6.1 Simulation design

To simulate event times closely following the observed data distributions, we employed a procedure involving first fitting Cox regression models to each (cause-specific) hazard and next fitting Weibull hazards to the baseline cumulative hazards with treatment-specific scale and shape parameters allowed change over time. This procedure is further described in the Supporting Information. On GitHub, plots of the resulting baseline hazard functions across time can be found as well.

To evaluate the performance of our estimation procedure, as well as competitors (see Section 6.3), we consider the following two variations over our simulation scenario:

**Setting 1:** Censoring allowed to depend on covariates and treatment; treatment distribution obtained from a logistic regression on the observed data, with main effects of all covariates.

**Setting 2:** Covariate-independent censoring, still with complex variation over time; randomized treatment (simulated with prevalence as in the observed data).

Covariate values are drawn randomly from the observed data. Note that for both settings, the censoring mechanism only depends on observed information so that coarsening at random holds.

### 6.2 Parameter of interest

We consider estimation of the average treatment effect parameter \( \Psi_\tau^{\text{ate}} : \mathcal{M} \to \mathbb{R} \) defined in terms of a contrast between two intervention-specific mean outcomes, namely, \( \Psi_\tau^{\text{ate}}(P) = \Psi_\tau^{\text{r}}(P) - \Psi_\tau^{\text{w}}(P) \), where \( \Psi_\tau^{\text{r}}(P) = E_{\pi^{\text{r}}}[T \leq \tau, \Delta = 1] \) and \( \pi^{\text{r}}(a \mid \ell) = 1\{a = a' \} \) for \( a' = 0, 1 \), evaluated at \( \tau = 10 \) years. For this parameter, the efficient influence function is simply given by

\[ D_\tau^{\text{ate}}(P)(O) = D_\tau^{\text{r}}(P)(O) - D_\tau^{\text{w}}(P)(O), \]

which we can also write on the form

\[ D_\tau^{\text{ate}}(P)(O) = \sum_{j=1}^{2} \int_0^{\tau} w_j^{\text{ate}}(\lambda_1, \lambda_2, \lambda^c, \pi) \]

\[ (A, L)(N_j(dt) - \mathbb{1}[T \geq t]\lambda_j(t \mid A, L)dt) \]

\[ + F_1(\tau \mid A, L) - \Psi_\tau^{\text{int}}(P), \]

not captured by models depending on the proportional hazards assumption.
with \( w_{\pi}^{\text{MLE}}(\lambda_1, \lambda_2, \lambda^c, \pi) = w_{\pi}^{\text{MLE}}(\lambda_1, \lambda_2, \lambda^c, \pi) - w_{\pi_0}^{\text{MLE}}(\lambda_1, \lambda_2, \lambda^c, \pi) \).

### 6.3 Considered estimators

We compare performance of the following different estimators:

1. A substitution estimator based on an Aalen–Johansen estimator for the cause one absolute risk function stratified by treatment arm.
2. A TMLE estimator based on a misspecified Cox model (including main effects of treatment and covariates, but no changepoint) for initial estimation of all hazards.
3. A TMLE estimator based on a random survival forest \(^{\text{Ishwaran et al., 2008}}\) (with default values of hyperparameters) for initial estimation of all hazards.
4. A TMLE estimator based on our implementation of the Poisson-based highly adaptive lasso estimator for initial estimation of all hazards. In one variation, we use a fixed and prespecified partitioning and in another we use cross-validation to choose the partitioning (adding only basis functions only as long as the cross-validated error is improved).
5. A discrete-time TMLE based on the survtmle package in R \(^{\text{Benkeser & Hejazi, 2019}}\), with the main results based on a discretization into a yearly grid. In one variation, we use logistic regression models for hazard estimation, with indicator functions for all time points and all main effects and interactions included in the true data-generating mechanism; in a similar variation, we use the same logistic regression models but leave out a covariate interaction; and in a final variation, we use a simple super learner incorporating, for example, a random forest.

In the Poisson-based highly adaptive lasso (HAL) estimator with a fixed partitioning, we used 18 grid points for the main effect of time, 15 for the interactions between time and treatment/covariates, 15 for the main effect of covariates, and 10 for the interactions between treatment/covariates.

### 6.4 Simulation results

Table 1 collects our simulation results. We make the following remarks:

1. The Aalen–Johansen estimator, being an unadjusted estimator, is seen to yield biased estimation under covariate-dependent censoring, and (to some extent) inefficient estimation under independent censoring and randomized treatment.
2. The RF-TMLE (the TMLE estimator using a random survival forest for initial estimation of all hazards) has low mean-squared error across both settings, but seemingly fails to generally produce unbiased estimates.
3. The HAL-TMLE (the TMLE estimator using the Poisson-based HAL estimator for initial estimation of all hazards) yields unbiased estimation and proper coverage. In the case where the Aalen–Johansen estimator is unbiased (with randomized treatment and independent censoring), the HAL improves mean-squared error by taking into account covariate information. Similar results are obtained with the two variations of the HAL estimator (on GitHub, further results on varying the grid used can also be found).
4. The discrete-time survival TMLE fails to generally provide reliable inference, whereas one version of the logistic regression models used in the initial estimation of the hazards results in unbiased estimation for the target parameter the other does not, and for both versions, the estimated standard errors of the estimators are much larger than the empirical standard deviations. We provide more results for different discretization schemes, as well as the results for initial estimation based on super learning, on GitHub.

### 7 Analysis of the dataset on follicular cell lymphoma

We apply the TMLE estimator with initial estimation based on the Poisson highly adaptive lasso estimator to the observed data on follicular cell lymphoma. We refer to the description of these data given in Section 6. As in Section 6, we consider estimation of the average treatment effect on the cause one specific absolute risk probability, evaluated at \( \tau = 10 \) years (see Section 6.2). For both cause-specific hazards as well as for the hazard of censoring, we use the Poisson-based HAL with a fixed partitioning (using, as in the simulations, 18 grid points for the main effect of time, 15 for the interactions between time and treatment/covariates, 15 for the main effect of covariates, and 10 for the interactions between treatment/covariates). After applying the TMLE step, we estimate that the average treatment effect comparing the combination treatment against radiation treatment alone is \(-0.0505\), corresponding to a 5% decrease in the absolute risk of relapse, with a 95% confidence interval of \((-0.187, 0.0866)\).

For comparison, we also computed the average treatment effect using Cox models including main effects of
TABLE 1  Results from the simulation settings with covariate-dependent censoring (upper panel) and covariate-independent censoring as well as randomized treatment (lower panel).

| Covariate-dependent censoring | HAL-SL TMLE | HAL TMLE | Cox TMLE | RF TMLE | AJ survtmle | survtmle GLM | survtmle GLM miss |
|-------------------------------|-------------|----------|----------|---------|-------------|--------------|------------------|
| bias                          | 0.0018      | 0.0021   | 0.0036   | 0.0136  | 0.0343      | 0.0019       | 0.0103           |
| SE                            | 0.0307      | 0.0308   | 0.0331   | 0.0302  | 0.0300      | 0.0411       | 0.0422           |
| SD                            | 0.0307      | 0.0307   | 0.0309   | 0.0296  | 0.0295      | 0.0284       | 0.0288           |
| MSE (x100)                    | 0.0940      | 0.0938   | 0.0953   | 0.0874  | 0.0869      | 0.0805       | 0.0829           |
| cov (95%)                     | 0.9460      | 0.9500   | 0.9560   | 0.9380  | 0.9460      | 0.9959       | 1.0000           |
| rel. MSE                      | 1.0817      | 1.8081   | 1.0963   | 1.0057  | 1.0000      | 0.9265       | 0.9541           |

| Covariate-independent censoring + randomized treatment | HAL-SL TMLE | HAL TMLE | Cox TMLE | RF TMLE | AJ survtmle | survtmle GLM | survtmle GLM miss |
|--------------------------------------------------------|-------------|----------|----------|---------|-------------|--------------|------------------|
| bias                                                   | 0.0004      | 0.0002   | -0.0001  | 0.0075  | 0.0006      | 0.0023       | 0.0025           |
| SE                                                     | 0.0271      | 0.0271   | 0.0276   | 0.0260  | 0.0279      | 0.0326       | 0.0336           |
| SD                                                     | 0.0272      | 0.0273   | 0.0278   | 0.0267  | 0.0276      | 0.0268       | 0.0273           |
| MSE (x100)                                             | 0.0740      | 0.0742   | 0.0772   | 0.0710  | 0.0759      | 0.0719       | 0.0744           |
| cov (95%)                                              | 0.9499      | 0.9500   | 0.9500   | 0.9380  | 0.9499      | 0.9819       | 0.9819           |
| rel. MSE                                               | 0.9745      | 0.9741   | 1.0131   | 0.9323  | 1.0000      | 0.9463       | 0.9802           |

0All results are obtained with sample size n = 2000 and M = 500 simulation repetitions. The true value of the target parameter (the average treatment effect) is −0.136. The first two columns (“HAL-SL” and “HAL”) show results for the TMLE estimator using the Poisson-based HAL estimator to estimate all (cause-specific) hazards (“HAL-SL” using an approach based on adding basis functions only as long as the cross-validated error is improved); the third column (“Cox”) shows results for the TMLE estimator using Cox regression to estimate all (cause-specific) hazards; the fourth column (“RF”) shows results for the TMLE estimator using a random survival forest to estimate all (cause-specific) hazards; the fifth column (“AJ”) shows results for an approach based on an Aalen–Johansen estimator (stratified by treatment); and the last columns (“survtmle”) show results for the discrete-time TMLE estimator based on logistic regression models for initial estimation (the results for the discrete-time TMLE using super learning for initial estimation can be found on GitHub).

all covariates to estimate both cause-specific hazards and the hazard of censoring. With this approach, we estimate from Step 1 (before applying the TMLE step) that the average treatment effect is −0.0920 and from Step 2 (after applying the TMLE step) that the average treatment effect is −0.0335. Previous analysis of the data conducted by Scheike and Zhang (2011) illustrates clearly the nonproportionality present in the data, explaining the bias we see here of the initial Cox approach. Otherwise, as can be found on GitHub, we achieved very similar results with the Poisson-HAL TMLE and with our TMLE procedure using the random survival forest for initial estimation.

8 | DISCUSSION

This work provides a TMLE procedure for classical continuous-time competing risks settings, including a data-adaptive estimation method for continuous-time hazards via highly adaptive lasso estimation. Importantly, our method constitutes a novel tool for machine-learning-based causal inference for continuous-time-to-event data that can be applied to analyze observational as well as randomized trial settings. Particularly, it provides a useful alternative to analyses reporting hazard ratios obtained from Cox regression models as a measure of a treatment effect, targeting instead causal parameters and requiring no model specification of nuisance parameters to achieve valid inference and efficiency.

Our simulations demonstrate that our TMLE estimator with initial estimation based on the implemented Poisson-based highly adaptive lasso estimator performs in agreement with the asymptotic theory, improving precision relative to the Kaplan–Meier approach and achieving proper coverage with a variance estimator based on the efficient influence function. In our simulations, we further employed an approach using our TMLE estimation procedure with random survival forests for initial estimation of all hazards as well as compared our continuous-time TMLE method with the existing discrete-time survival TMLE (applied to a discretized version of the data). Both these methods generally failed to provide reliable inference in terms of standard error estimation and proper coverage confidence intervals. For the random forest approach, however, we do emphasize that it is possible that tuning of forest hyperparameters would lead to better results; for example, different splitting rules specific for the competing risks setting (Ishwaran et al., 2014) may make a big difference for the performance.

We remark that there is still work to be done to improve the implementation of the highly adaptive lasso in full generality. In its place, we note that the currently
implemented targeting algorithms could also be coupled with initial estimators based on any Cox regression model or on a super learner (van der Laan et al., 2007) combining, for example, different Cox models, or different variants of the random survival forest, into one estimator. As considered by Rytgaard and van der Laan (2022), one may also implement a version of the highly adaptive lasso estimator based on the Cox model itself; however, that approach does not allow for smoothing dependence on time, nor does it fit into the (Lebesgue) log-likelihood cross-validation scheme that we suggest. Moreover, it is important to remark that our theoretical results on the highly adaptive lasso rely on using the Cauchy–Schwarz inequality to provide an upper bound on the second-order remainder, which only works for continuous estimators for the hazard; in future work, we will look into equivalent results for discrete estimators.

**DATA AVAILABILITY STATEMENT**

The data that support our findings are available in R from the rfsrc package (Ishwaran & Kogalur, 2022), see https://github.com/kogalur/randomForestSRC/blob/master/src/main/resources/cran/data/follic.txt.

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**REFERENCES**

Andersen, P.K., Borgan, Ø., Gill, R.D. & Keiding, N. (1993) *Statistical models based on counting processes*. New York: Springer.

Andersen, P.K., Syriopoulou, E. & Parner, E.T. (2017) Causal inference in survival analysis using pseudo-observations. *Statistics in Medicine*, 36(17), 2669–2681.

Benkeser, D., Carone, M. & Gilbert, P.B. (2018) Improved estimation of the cumulative incidence of rare outcomes. *Statistics in Medicine*, 37(2), 280–293.

Benkeser, D. & Hejazi, N. (2019) survtmlc: compute targeted minimum loss-based estimates in right-censored survival settings. R package version 1.1.1.

Bibaut, A.F. & van der Laan, M.J. (2019) Fast rates for empirical risk minimization over càdlàg functions with bounded sectional variation norm. arXiv e-prints, arXiv:1907.09244.

Bickel, P.J., Klaassen, C.A.J., Ritov, Y. & Wellner, J.A. (1993) *Efficient and adaptive inference in semiparametric models*. Baltimore: Johns Hopkins University Press.

Cai, W. & van der Laan, M.J. (2019) One-step targeted maximum likelihood estimation for time-to-event outcomes. *Biometrics*, 76, 722–733.

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

Ferreira Guerra, S., Schnitzer, M.E., Forget, A. & Blais, L. (2020) Impact of discretization of the timeline for longitudinal causal inference methods. *Statistics in Medicine*, 39(27), 4069–4085.

Fine, J.P. & Gray, R.J. (1999) A proportional hazards model for the subdistribution of a competing risk. *Journal of the American Statistical Association*, 94(446), 496–509.

Gill, R.D. & Robins, J.M. (2001) Causal inference for complex longitudinal data: the continuous case. *The Annals of Statistics*, 29(6), 1785–1811.

Gill, R.D., van der Laan, M.J. & Wellner, J.A. (1995) Inefficient estimators of the bivariate survival function for three models, Ann. Inst. Henri Poincaré. 31, 545–597.

Gray, R.J. (1988) A class of k-sample tests for comparing the cumulative incidence of a competing risk. *The Annals of Statistics*, 16(3), 1141–1154.

Hernan, M.A. & Robins, J.M. (2020) Causal inference. Boca Raton, FL: Chapman & Hall/CRC.

Hubbard, A.E., van der Laan, M.J. & Robins, J.M. (2000) Non-parametric locally efficient estimation of the treatment specific survival distribution with right censored data and covariates in observational studies. In: Halloran, M.E. & Berry, D.A. (Eds.) *Statistical models in epidemiology, the environment, and clinical trials*. New York: Springer, pp. 135–177.

Ishwaran, H., Gerds, T.A., Kagulor, U.B., Moore, R.D., Gange, S.J. & Lau, B.M. (2014) Random survival forests for competing risks. *Biostatistics*, 15(4), 757–773.

Ishwaran, H. & Kogalur, U. (2022) *Fast unified random forests for survival, regression, and classification (RF-SRC)*. R package version 3.1.0.

Ishwaran, H., Kagulor, U.B., Blackstone, E.H. & Lauer, M. (2008) Random survival forests. *Annals of Applied Statistics*, 2(3), 841–860.

Lindsey, J.K. (1995) Fitting parametric counting processes by using log-linear models. *Journal of the Royal Statistical Society: Series C (Applied Statistics)*, 44(2), 201–212.

Moore, K.L. & van der Laan, M.J. (2009a) Application of time-to-event methods in the assessment of safety in clinical trials. In: Peace, K.E. (Ed.) *Design and analysis of clinical trials with time-to-event endpoints*. London: Taylor & Francis, pp. 455–482.

Moore, K.L. & van der Laan, M.J. (2009b) Covariate adjustment in randomized trials with binary outcomes: targeted maximum likelihood estimation. *Statistics in Medicine*, 28(1), 39–64.

Moore, K.L. & van der Laan, M.J. (2009c) Increasing power in randomized trials with right censored outcomes through covariate adjustment. *Journal of Biopharmaceutical Statistics*, 19(6), 1099–1131.

Ozenne, B.M.H., Scheike, T.H., Sterk, L. & Gerds, T.A. (2020) On the estimation of average treatment effects with right-censored time to event outcome and competing risks. *Biometrical Journal*, 62(3), 751–763.

Robins, J. (1986) A new approach to causal inference in mortality studies with a sustained exposure period-application to control of the healthy worker survivor effect. *Mathematical Modelling*, 7(9–12), 1393–1512.

Robins, J.M. & Rotnitzky, A. (1992) Recovery of information and adjustment for dependent censoring using surrogate markers. In: Jewell, N., Dietz, K. & Farewell, V. (Ed.) *AIDS epidemiology - methodological issues*. Boston, MA: Springer, pp. 297–331.

Rytgaard, H.C., Gerds, T.A. & van der Laan, M.J. (2022) Continuous-time targeted minimum loss-based estimation of intervention-specific mean outcomes. *The Annals of Statistics*, 50(5), 2469–2491.
SUPPORTING INFORMATION

Web appendices referenced in Sections 1, 2.1, 3.1, 3.2, 5.2, 5.3, and 6.1 along with code are available with this paper at the Biometrics website on Wiley Online Library. The web appendices include: i) the proof of causal interpretability of the target parameter; ii) extra details on the simulation procedure; iii) proof of Theorem 1 of the main paper; iv) derivation of the efficient influence function and of the second-order remainder for the survival analysis setting; v) derivation of the efficient influence function and of the second-order remainder for the competing risks setting; vi) arguments for implementing the highly adaptive lasso estimator with Poisson regression, results on controlling the second-order remainder given the highly adaptive lasso rate and proof of Lemma 1. Sample code, extra simulation results, and plots of the dependence of hazards on time used in the simulation can all be found on GitHub: https://github.com/helenecharlotte/Web-appendix-iterative-competing-risks-tmle.

Data S1

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