Estimation de l'Effet Moyen du Traitement (ATE) en survie causale: Comparaison, Applications et Recommandations Pratiques

Charlotte Voinot [1] & Julie Josse [2] & Bernard Sebastien [3]

[1] *INRIA - SANOFI, France, charlotte.voinot@sanofi.com*
[2] *INRIA, France, julie.josse@inria.fr*
[3] *SANOFI, France, bernard.sebastien@sanofi.com*

Résumé. L'estimation de l'effet Moyen du traitement (ATE) constitue l'une des mesures fondamentales en inférence causale visant à évaluer l'impact causal d'un traitement sur une variable de résultat. L'analyse de survie causale se positionne au cœur de cette démarche en cherchant à évaluer l'effet d'un traitement sur la survie des patients au cours du temps. Cependant, malgré l'abondance de littérature en survie causale, l'utilisation des méthodes de Cox demeure prédominante pour évaluer cet effet. Ainsi, l'objectif principal de cette recherche est d'estimer l'effet causal d'un traitement en utilisant des données de survie qui ne proviennent pas forcément d'essais randomisés. Elle entend principalement fournir des recommandations pratiques aux utilisateurs face à la multitude d'informations disponibles ainsi que de mettre en lumière les avantages et les différences par rapport aux approches classiques encore largement utilisées. Pour cela, dans un premier temps, un état de l'art des méthodes de survie causale sera présenté en décrivant les hypothèses d'identifiabilité et les principaux estimateurs, dont les méthodes de pondération, de régression et les approches doublement/triplement robustes. Parmi ces méthodes, on trouve des estimateurs paramétriques, semi-paramétriques et non paramétriques comme les forêts de survie causale. Par la suite, une étude extensive par simulation sera réalisée pour comparer les différents estimateurs, leurs régimes de prédilection et illustrer leurs propriétés théoriques sur des échantillons de taille finie. Pour finir, nous examinerons comment l'ajout de certaines variables dans les modèles de censure, de survie ou de traitement peut impacter la variance des estimateurs.

Mots-clés. Survie causale, inférence causale, ATE, données censurées

Abstract. Estimating the Average Treatment Effect (ATE) is one of the fundamental measures in causal inference, aimed at assessing the causal impact of a treatment on an outcome variable. Causal survival analysis is at the heart of this approach, seeking to evaluate the effect of a treatment on patient survival over time. However, despite the abundance of literature on causal survival, the use of Cox methods remains predominant for assessing this effect. Thus, the main objective of this research is to estimate the causal effect of a treatment using survival data not necessarily derived from randomized trials. Its main aim is to provide users with practical recommendations in the face of the multitude of information available, and to highlight the advantages and differences compared with the classic approaches still widely used. To this end, we will begin by presenting the state of the art in causal survival methods, describing identifiable assumptions and the main estimators, including weighting, regression and triply/doubly robust approaches. These methods include parametric, semi-parametric and non-parametric estimators such as causal survival forests.An extensive simulation study

will then be carried out to compare the different estimators, their preferred regimes and illustrate their theoretical properties on finite sample sizes. Finally, we will examine how the addition of certain variables in the censoring, survival or treatment models can impact the variance of the estimators.

Keywords. Causal survival, causal inference, average treatment effect, censoring

1 Background

Causal survival analysis can be seen as the combination of causal analysis and survival analysis: the aim is to assess the causal effect of a treatment on a outcome which is a time until an event occurs. The objective of this article is to provide a comprehensive overview of the different available methods to estimate the (average) effect of a treatment on survival.

1.1 Notation

Let's consider a sample of n i.i.d observations that are described by:

- X_i: the covariates, $X \in \mathbb{R}^p$
- A_i: the binary treatment, $A \in \{0, 1\}$
- C_i: the time to censoring, $C \in \mathbb{R}^+$
- $T_i(0)$: the survival time to the event of interest had the patient received control $A_i = 0$
- $T_i(1)$: the survival time to the event of interest had the patient received treatment $A_i = 1$
- $T_i = A_i T_i(1) + (1 - A_i) T_i(0)$, $T \in \mathbb{R}^+$: the observed outcome corresponds to the potential outcome under the assigned treatment; this is known as the consistency identifiability assumption in causal inference
- $\Delta_i = I\{T_i \leq C_i\}$ the status of censoring, where $I\{\cdot\}$ is the indicator
- $\tilde{T}_i = T_i \wedge C_i = \min(T_i, C_i)$, the observed time. When an observation is censured, then its observed time is equal to the censoring time

The observed data can be summarized as a quadruplet $(X_i, A_i, \Delta_i, \tilde{T}_i)$ represented in Table 1.

1.2 Treatment effect

In causal inference, the primary goal is to estimate the individual causal effect of the treatment denoted as $\theta_i = T_i(1) - T_i(0)$ (Rubin, 1974). However, this quantity cannot be observed

Table 1: Example of survival data

	Covariates			Treatment	Censoring	Status	Outcomes		
ID	X_1	X_2	X_3	**A**	**C**	Δ	**T(0)**	**T(1)**	$\tilde{T}$
1	1	1,5	4	1	?	1	?	200	200
2	5	1	2	0	?	1	100	?	100
3	9	0,5	3	1	200	0	?	?	200

because at most one outcome can be observed per sample (see Table 1). Furthermore, censoring may also mask outcomes (Turkson et al., 2021). Despite these challenges, certain identifiability assumptions enable us for estimating the average treatment effect (Díaz et al., 2019; Ozenne et al., 2020) (ATE) which is defined as follows:

Definition 1 (Causal effect: **Average treatment effect** in survival analysis (ATE))**.**

$$\theta = \mathbb{E}\left[y(T(1)) - y(T(0))\right]$$

where $y(T)$ is some deterministic transformation of the survival time T such as:

- *$y(T) = I\{T > t\}$ for $t \leq \tau$; then, $E(y(T))$ becomes the survival probability at time t.*
- *$y(T) = T \wedge \tau = \min(T, \tau)$ with τ a fixed time horizon; then, $E(y(T))$ becomes the restricted mean survival time (RMST) at time τ (Chen and Tsiatis, 2001).*

Definition 2 (Causal effect: Difference between **survival probabilities**)**.**

$$\theta(t) = E[I\{T(1) > t\} - I\{T(0) > t\})] = S_1\{t) - S_0(t)$$

with $S_a(t) = P(T(a) > t)$, the probability of surviving at time t when treatment $A = a$.

Definition 3 (Causal effect: Difference of **restricted mean survival time (RMST)** between treated and controls)**.**

$$\theta_{RMST}(\tau) = \mathbb{E}\left[T(1) \wedge \tau - T(0) \wedge \tau\right]$$

Survival probabilities and RMST are linked as follows:

$$\theta_{RMST}(\tau) = \int_0^\tau \left(S_1(t) - S_0(t)\right) dt$$

RMST can be interpreted as the average survival time from baseline to a pre-specified time τ: a RMST value of 10 days with $\tau = 200$ means that on average the treatment increases the survival time by 10 days at 200 days.

In this paper, we focus on θ_{RMST} as the estimand of interest. The aim is to construct estimators of this average causal effect while overcoming potential biases due to confounding factors and to right censoring.

1.3 Censoring mechanism

Two different assumptions about the censoring mechanism can be considered.

Assumption 1 (**Independent/ Non informative censoring**).

$$C \perp\!\!\!\perp T(0), T(1), X, A$$

Under Assumption 1, subjects censored at time t are representative of all subjects who remain at risk at time t. Therefore, the probability of experiencing an event should be the same for both censored subjects and subjects remaining at risk. It is as if the censored subjects were randomly selected from all subjects.

Assumption 2 (**Conditionally independent censoring**).

$$C \perp\!\!\!\perp T(0), T(1) | X, A$$

Under Assumption 2, within subgroups represented by $X = x$, subjects censored at time t are representative of all subjects in their subgroup who remain at risk at time t. It is as if the censored subjects were randomly selected inside each subgroup. This assumption is also referred to as dependent censoring.

But another assumption for identifiability of RMST is required under Assumption 2: we need to assume that all subjects have a positive probability to remain uncensored at their failure time.

Assumption 3 (**Positivity / Overlap for censoring**).

$$pr(C > t \mid X = x, A = a) > 0, \quad \textit{for the identifiability of RMST: } t \leq \tau.$$

If for a time t, $\mathbb{P}(C > t \mid X = x, A = a) = 0$, then this excludes that we have any observed outcomes after time t. For example, if we consider a clinical trial with administrative censoring after one year of study, then the probability of remaining uncensored after one year is zero. In that case, the potential outcomes $T(0)$ and $T(1)$ are not observed at all after $t = 1$ year. One can consider lowering the threshold time τ such that each subject has a probability of remaining uncensored at their restricted time.

2 Causal survival analysis with a Randomized Control Trial

Randomized clinical trials (RCTs) are the gold standard for establishing the effect of a treatment on an outcome, because treatment allocation is under control, which ensures (asymptotically) the balance of covariates between treated and controls, and thus avoids problems of confounding between covariables and treatment.

The core assumption in a RCT is the random assignment of the treatment (Rubin, 1974).

Assumption 4 (**Random treatment assignment**).

$$A \perp\!\!\!\perp (T(0), T(1), X)$$

Assumption 4 implies that the treatment is given at random and is independent of both the potential outcomes and the covariates.

Indentifiability. Under Assumptions 4 (random treatment assignment) and 1 (independent censoring), the RMST can be identified as follows:

$$\begin{aligned}
\theta_{RMST} &= \mathbb{E}[T(1) \wedge \tau - T(0) \wedge \tau] = \int_0^\tau \mathbb{E}[I\{T(1) > t\} - I\{T(0) > t\}]dt && \text{(Independent censoring)} \\
&= \int_0^\tau \mathbb{E}[I\{T(1) > t | A = 1\} - \mathbb{E}[I\{T(0) > t | A = 0\}dt && \text{(Random treatment assignment)} \\
&= \int_0^\tau \mathbb{E}[I\{T > t | A = 1\} - \mathbb{E}[I\{T > t | A = 0\}]dt && \text{(Consistency)} \\
&= \int_0^\tau S(t|A = 1) - S(t|A = 0)dt
\end{aligned} \tag{1}$$

where $S(t|A = a)$ is the survival function of the population with treatment $A = a$.

Under Assumptions 4 (random treatment assignment) and 2 (conditionally independent censoring), the RMST can be identified as follows:

$$\begin{aligned}
\theta_{RMST} &= \int_0^\tau \mathbb{E}[I\{T > t | A = 1, X\}] - \mathbb{E}[I\{T > t | A = 0, X\}]dt && \text{(Consistency)} \\
&= \int_0^\tau \mathbb{E}\left[\frac{I\{T > t | A = 1\} * \Delta}{S_c(t|X, A = 1)} - \frac{I\{T > t | A = 0\} * \Delta}{S_c(t|X, A = 0)}\right] dt && \text{(Conditionally independent censoring)}
\end{aligned} \tag{2}$$

where $S_c(t|X, A = a)$ is the survival function of remain uncensored given the covariate X_i

2.1 Estimation under independent censoring

2.1.1 Non adjusted Kaplan meier estimator

Definition 4 (Unadjusted kaplan meier estimator)**.**

$$\hat{S}_{KM}(t \mid a) == \prod_{j=1, t_j <= t} \left(1 - \frac{\sum_i I\left\{\tilde{T}_i = t_j, \Delta_i = 1, A_i = a\right\}}{\sum_i I\left\{\tilde{T}_i \geq t_j, A_i = a\right\}}\right)$$

Unadjusted Kaplan meier which maximizes the likelihood of the observations is a uniformly consistent non parametric estimator for estimating the survival function (Gill, 1983) and (Kaplan and Meier, 1958).

The corresponding RMST is obtained in integrating from 0 to τ the difference between non adjusted kaplan meier estimator of the treated and controls (1).

2.2 Estimation under conditional censoring

Under Assumptions 4 (random treatment assignment), 2 (conditional censoring) and 3 (censoring positivity), the unadjusted KM estimator overestimates the real survival probabilities (Willems et al., 2018). Thus, correction for the presence of dependent censoring is important in order to obtain a good estimator. Under these assumptions, the adjusted IPCW (inverse probability of censoring weighting) Kaplan meier estimator (Robins and Rotnitzky, 1992; Robins and Finkelstein, 2000) can be used to estimate the causal treatment effect.

2.2.1 (IPCW) adjusted Kaplan meier estimator

Definition 5 (IPCW adjusted kaplan meier estimator)**.**

$$\hat{S}_{IPCW-KM}(t \mid a) = \prod_{j=1, t_j <= t} \left(1 - \frac{\sum_i \hat{w}_i(t_j, X_i) * I\left\{T_i = t_j, C_i \geq t_j, A_i = a\right\}}{\sum_i \hat{w}_i(t_j, X_i) * I\left\{T_i \geq t_j, C_i \geq t_j, A_i = a\right\}}\right)$$

- $\hat{w}_i(t, X_i) = \frac{1}{\hat{S}_c(t|X_i, A_i)}$ *is the inverse of probability of remain uncensored given* X_i*.*
- $\hat{S}_c(t|X_i, A_i)$ *is based on the fit of semi-parametric or parametric model for censoring (for example a Cox model) with* X_i *and* A_i *the covariates.*

This estimator gives extra weight to subjects who are not censored. At every time point t, each subject i is given a weight which is inversely proportional to the estimated probability of having remained uncensored until time t.

In the same way than before, the corresponding RMST is obtained in integrating from 0 to τ the difference between adjusted kaplan meier estimator of the treated and controls (2).

3 Causal survival analysis with an observational study

In the context of observational study, Assumption 4 (randomized treatment assignment) is no longer verified. Some additional assumptions are required to identify θ_{RMST}. These assumptions are classical for causal inference with observational data:

Assumption 5 (**Conditional exchangeability / Uncounfoundedness**).

$$A \perp\!\!\!\perp (T(0), T(1))|X$$

with X the set of covariates that are related both to treatment's assignment and outcomes.

Under Assumption 5, the treatment assignment is randomly assigned conditionally on the covariates X. It is as if the treatment for all subjects were randomly selected inside each subgroup.

Assumption 6 (**Positivity / Overlap for treatment**).

$$1 > P(A = a \mid X = x) > 0$$

Identifiability. Under assumption 5 (Uncounfoundedness) and 1 (Independent censoring), the RMST can be identified as follows:

$$\begin{aligned}
\theta &= \mathbb{E}[T(1) \wedge \tau - T(0) \wedge \tau] \\
&= \int_0^\tau \mathbb{E}\left[I\{T(1) > t\} * \frac{A}{e(X)} - I\{T(0) > t\} * \frac{1-A}{1-e(X)} \right] dt \text{ (Identifiability of the IPTW)} \\
&= \int_0^\tau \mathbb{E}\left[I\{T > t \mid A = 1\} * \frac{A}{e(X)} - I\{T > t \mid A = 0\} * \frac{1-A}{1-e(X)} \right] dt \text{ (By consistency)}
\end{aligned} \tag{3}$$

Under assumption 5 (Uncounfoundedness) and 2 (conditionally independent censoring), the RMST can be identified as follows:

$$\begin{aligned}
\theta &= \mathbb{E}\left[(T \wedge \tau) \left(\frac{A}{e(X)} - \frac{1-A}{1-e(X)} \right) \right] \text{ (Identifiability of the IPTW)} \\
&= \mathbb{E}\left[\mathbb{E}[(T \wedge \tau) \mid A, X] \left(\frac{A}{e(X)} - \frac{1-A}{1-e(X)} \right) \right] \\
&= \mathbb{E}\left[\frac{\widetilde{T} \wedge \tau \cdot \Delta^\tau}{S_C(\widetilde{T} \wedge \tau \mid A, X)} \left(\frac{A}{e(X)} - \frac{1-A}{1-e(X)} \right) \right]
\end{aligned} \tag{4}$$

Under the same assumptions, it can be identified also as g-formula:

$$\begin{aligned}
\theta &= \mathbb{E}\left[T(1) \wedge \tau - T(0) \wedge \tau \right] \\
&= \mathbb{E}\left[\mathbb{E}\left[T(1) \wedge \tau \mid X, A = 1 \right] - \mathbb{E}\left[T(0) \wedge \tau \mid X = X, A = 0 \right] \right] \text{ (Uncounfoundedness)} \\
&= \mathbb{E}\left[\mathbb{E}\left[T \wedge \tau \mid X, A = 1 \right] - \mathbb{E}\left[T \wedge \tau \mid X, A = 0 \right] \right] \text{ (Consistency)}
\end{aligned} \tag{5}$$

3.1 Estimation under independent censoring

3.1.1 IPTW Kaplan meier estimator

Under Uncounfoundedness and independent censoring (Assumptions 5 and 1), the Kaplan meier estimator has to include a weighting term to take into account that the treated and control groups are unbalanced. This weighted estimator is called the inverse probability of treatment weighted Kaplan meier estimator (IPTW-KM) (Xie and Liu, 2005).

Based on the identifiability (3), the IPTW KM is defined as:

Definition 6 (Adjusted IPTW kaplan meier estimator)**.**

$$\hat{S}_{IPTW-KM}(t \mid a) = \prod_{j=1, t_j <= t} \left(1 - \frac{\sum_i \hat{w}_i * I\left\{T_i = t_j, C_i \geq t_j, A_i = a\right\}}{\sum_i \hat{w}_i * I\left\{T_i \geq t_j, C_i \geq t_j, A_i = a\right\}}\right)$$

with $\hat{w}_i = \frac{A_i}{\hat{e}(X_i)} + \frac{1-A_i}{1-\hat{e}(X_i)}$ *the inverse of the propensity score.*

In the exact same way than before, the corresponding RMST is obtained in integrating from 0 to τ the difference between IPTW adjusted kaplan meier estimator of the treated and controls (3).

3.2 Estimation under conditionally independent censoring

3.2.1 Inverse probability of weighting estimation (IPTW-IPCW)

When the independent censoring assumption is not verified, the IPTW-IPCW Kaplan meier estimator can be used to estimate the causal treatment effect . The IPTW-IPCW KM estimator is a combination of both estimators (Anstrom and Tsiatis, 2004): IPTW to overcome that the treatment allocation is not random and IPCW to overcome the dependent censoring.

Based on the identifiability (4), the IPTW-IPCW is defined as:

Definition 7 (IPTW-IPCW estimator)**.**

$$\widehat{\theta}_{\text{IPTW-IPCW}}(\tau) = \frac{1}{n} \sum_{i=1}^{n} \frac{\Delta_i^{\tau} \cdot \tilde{T}_i \wedge \tau}{\hat{S}_C\left(\widetilde{T} \wedge \tau \mid A_i, X_i\right)} \left(\frac{A_i}{\hat{e}\left(X_i\right)} - \frac{1 - A_i}{1 - \hat{e}\left(X_i\right)}\right)$$

where $\hat{S}_C\left(\widetilde{T} \wedge \tau \mid A_i, X_i\right)$ *is a semi parametric (or parametric) methodology to estimate the survival function of remain uncensored.*

It enables a balance between treatment and control groups and between censored and uncensored individuals.

This RMST estimator can be obtained at first in estimating the survival function of

remain uncensored in using semi-parametric or parametric model. Then, the weight for each observation can be computed as:

$$w_i = \frac{\Delta_i^\tau}{\hat{S}_C\left(\widetilde{T} \wedge \tau \mid A_i, X_i\right)} * \left(\frac{A_i}{\hat{e}\left(X_i\right)} - \frac{1 - A_i}{1 - \hat{e}(X_i)}\right)$$

An adjusted kaplan estimator (weighted by the previous w_i) can be fitted for $A = 1$ and $A = 0$ (see definition 8).

Definition 8 (Adjusted IPTW-IPCW kaplan meier estimator)**.**

$$\hat{S}_{IPTW-IPCW-KM}(t \mid a) = \prod_{j=1, t_j <= t} \left(1 - \frac{\sum_i \hat{w}_i(t, X_i) * I\left\{T_i = t_j, C_i \geq t_j, A_i = a\right\}}{\sum_i \hat{w}_i(t, X_i) * I\left\{T_i \geq t_j, C_i \geq t_j, A_i = a\right\}}\right)$$

with $\hat{w}_i(t, X_i) = \frac{1}{\hat{S}_C\left(\widetilde{T} \wedge \tau | A_i, X_i\right)} * \left(\frac{A_i}{\hat{e}(X_i)} + \frac{1 - A_i}{1 - \hat{e}(X_i)}\right)$ *the corresponding weight including the inverse of the propensity score and the inverse probability of remain uncensored given the covariates.*

Then, the corresponding RMST is the integral of the difference between the survival curve with $A = 1$ and the $A = 0$.

3.2.2 G-formula plug-in estimator

Another possible estimator under assumption 5 and 2 is the G-formula plug-in estimator.

It is an alternative of IPCW in leveraging the regression formulation. Instead of fitting a model for the censored mechanism and a model for the probability of being treated, the corresponding estimators fit a model of the conditional outcome mean. Applying these models to the each treatment arm, and then marginalizing over the empirical covariates distributions of the target population, gives the corresponding expected outcome (Robins, 1986). Based on the g-formula identifiability (5), this outcome model based estimator is defined as:

Definition 9 (G-formula plug-in estimator)**.**

$$\widehat{\theta}_{g\text{-}formula}\left(\tau\right) = \frac{1}{n} \sum_{i=1}^{n} \left(\hat{F}\left(X_i, 1\right) - \hat{F}\left(X_i, 0\right)\right)$$

with $F(x, a) \triangleq \mathbb{E}[T \wedge \tau \mid X = x, A = a]$*. It can be estimated in using semi-parametric or parametric methods.*

Generally, $F(x, a)$ estimator is based on the estimation of the conditional survival function. It can be obtained in fitting one semi-parametric (or parametric) model (i.e. Cox model) by treatment on the corresponding observations and in predicting the results for the all observations. Then, the RMST is computed by the integral of the difference between the predicted conditional survival curve with A=1 and A=0.

References

Anstrom, K. J. and A. A. Tsiatis (2004, 05). Utilizing Propensity Scores to Estimate Causal Treatment Effects with Censored Time-Lagged Data. *Biometrics 57*(4), 1207–1218.

Chen, P.-Y. and A. A. Tsiatis (2001). Causal inference on the difference of the restricted mean lifetime between two groups. *Biometrics 57*(4), 1030–1038.

Díaz, I., E. Colantuoni, D. F. Hanley, and M. Rosenblum (2019, July). Improved precision in the analysis of randomized trials with survival outcomes, without assuming proportional hazards. *Lifetime data analysis 25*(3), 439—468.

Gill, R. (1983). Large Sample Behaviour of the Product-Limit Estimator on the Whole Line. *The Annals of Statistics 11*(1), 49 – 58.

Kaplan, E. L. and P. Meier (1958). Nonparametric estimation from incomplete observations. *Journal of the American Statistical Association 53*(282), 457–481.

Ozenne, B. M. H., T. H. Scheike, L. Stærk, and T. A. Gerds (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), 1393–1512.

Robins, J. M. and D. M. Finkelstein (2000). Correcting for noncompliance and dependent censoring in an aids clinical trial with inverse probability of censoring weighted (ipcw) log-rank tests. *Biometrics 56*(3), 779–788.

Robins, J. M. and A. Rotnitzky (1992). *Recovery of Information and Adjustment for Dependent Censoring Using Surrogate Markers*, pp. 297–331. Boston, MA: Birkhäuser Boston.

Rubin, D. B. (1974, October). Estimating causal effects of treatments in randomized and nonrandomized studies. *Journal of Educational Psychology 66*(5), 688–701.

Turkson, A., F. ayiah mensah, and V. Nimoh (2021, 09). Handling censoring and censored data in survival analysis: A standalone systematic literature review. *International Journal of Mathematics and Mathematical Sciences 2021*, 1–16.

Willems, S., A. Schat, M. van Noorden, and M. Fiocco (2018). Correcting for dependent censoring in routine outcome monitoring data by applying the inverse probability censoring weighted estimator. *Statistical Methods in Medical Research 27*(2), 323–335. PMID: 26988930.

Xie, J. and C. Liu (2005). Adjusted kaplan–meier estimator and log-rank test with inverse probability of treatment weighting for survival data. *Statistics in Medicine 24*(20), 3089–3110.