Semiparametric Piecewise Proportional Hazards Model for Characterizing Treatment Effects in Immune-Oncology Clinical Trials

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Motivation

- In immune-oncology clinical trials, a lag time in treatment effect has been observed.
- This suggests a **change-point** in the onset of treatment effect.
- Patients who die or are censored before the change-point cannot benefit from the treatment.
- The semiparametric piecewise accelerated failure time model addresses this issue.

(Sunami and Hattori, 2026)

Purpose

- The issue is handled with an alternative semiparametric piecewise Cox model.

(Ozaki and Ninomiya, 2023)

- We develop inference procedures for the baseline hazard and change-point, not addressed by Ozaki and Ninomiya (2023), and characterize patient-specific treatment effects.

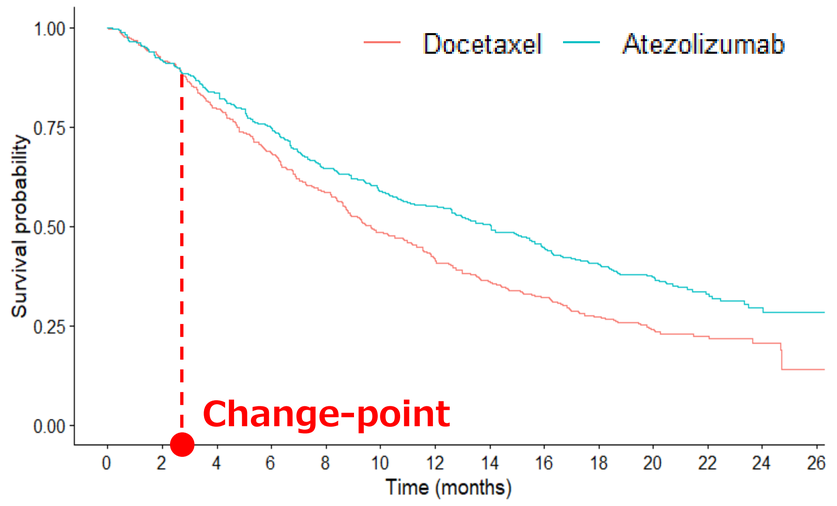


Figure: Kaplan-Meier curves for overall survival in Oak study (Rittmeyer et al., 2017).

Notation

- T : Survival time
- C : Censoring time
- Z : Assigned treatment (1: Test, 0: Control)
- $\boldsymbol{X}$: Covariate vector
- τ : Change-point (= Immune response onset time)

We consider a confirmatory randomized clinical trial and assume $T \perp\!\!\!\perp C | Z, \boldsymbol{X}$.

Proposed model

Semiparametric piecewise proportional hazards model

For the conditional hazard function $\lambda(t|Z, \boldsymbol{X})$,

$$\lambda(t|Z,\boldsymbol{X}) = \begin{cases} \lambda_0(t)\exp\left(\boldsymbol{\beta}^\top \boldsymbol{X}\right), & 0 \le t < \tau, \\ \lambda_0(t)\exp\left(\alpha Z + \boldsymbol{\beta}^\top \boldsymbol{X} + \boldsymbol{\gamma}^\top \boldsymbol{X} Z\right), & t \ge \tau, \end{cases}$$

- $\lambda_0(t)$: Baseline hazard function
- α : Treatment effect
- $\boldsymbol{\beta}$: Covariate effect
- $\boldsymbol{\gamma}$: Treatment – covariate interaction effect

Main results

Confidence interval (CI) for the change-point

- From Ozaki and Ninomiya (2023), under the condition that $\boldsymbol{\theta}^{(1)} - \boldsymbol{\theta}^{(2)} = \boldsymbol{\delta}/\sqrt{a_n},\ O(1) \neq a_n = o(n)$, where $\boldsymbol{\theta}^{(1)} := (\boldsymbol{\beta}^\top, 0, \mathbf{0}^\top)^\top$, $\boldsymbol{\theta}^{(2)} := (\boldsymbol{\beta}^\top, \alpha, \boldsymbol{\gamma}^\top)^\top$, and $\boldsymbol{\delta}$ is a constant vector, we have

$$\frac{n}{a_n}(\hat{\tau} - \tau_0) \xrightarrow{d} \operatorname{argmax}_{s\in\mathbb{R}} V_s^{*(1)}.$$

- $V_s^{*(1)} \equiv V_s\left\{\frac{1}{2}\boldsymbol{\delta}^\top \boldsymbol{A}^{*(1)}\boldsymbol{\delta},\ \frac{1}{2}\boldsymbol{\delta}^\top \boldsymbol{A}^{*(2)}\boldsymbol{\delta},\ (\boldsymbol{\delta}^\top \boldsymbol{A}^{*(1)}\boldsymbol{\delta})^{1/2},\ (\boldsymbol{\delta}^\top \boldsymbol{A}^{*(2)}\boldsymbol{\delta})^{1/2}\right\}$, where $V_s(c_1, c_2, \sigma_1, \sigma_2)$ is a Brownian motion with drift coefficients (c_1, c_2) and diffusion coefficients (σ_1, σ_2), and $\boldsymbol{A}^{*(j)}$ is the Fisher information matrix.

- The distribution function of $S = \operatorname{argmax}_{s\in\mathbb{R}} V_s(c_1, c_2, \sigma_1, \sigma_2)$ is

$$F\left(s;\ \frac{c_1}{\sigma_1}, \frac{c_2\sigma_1}{\sigma_2^2}, \frac{c_2}{\sigma_2}, \frac{c_1\sigma_2}{\sigma_1^2}\right) = \begin{cases} H\left(-s;\ \frac{c_1}{\sigma_1}, \frac{c_2\sigma_1}{\sigma_2^2}\right), & s < 0, \\ 1 - H\left(s;\ \frac{c_2}{\sigma_2}, \frac{c_1\sigma_2}{\sigma_1^2}\right), & s \ge 0, \end{cases}$$

where

$$H(s;\ \theta_1,\ \theta_2) = 2\left\{\theta_1^2 s + 1 + \frac{\theta_1^2}{2\theta_2(\theta_1+\theta_2)}\right\}\Phi(-\theta_1\sqrt{s}) - 2\theta_1\sqrt{s}\phi(\theta_1\sqrt{s}) - \frac{\theta_1(\theta_1+2\theta_2)}{\theta_2(\theta_1+\theta_2)}\exp\left\{2\theta_2(\theta_1+\theta_2)s\right\}\Phi(-(\theta_1+2\theta_2)\sqrt{s}).$$

- The CI for the change-point can be analytically estimated from F.
- The order of a_n does not affect the estimation of CI.

Characterization of treatment effects

- Patient-specific treatment effect (*TE*)

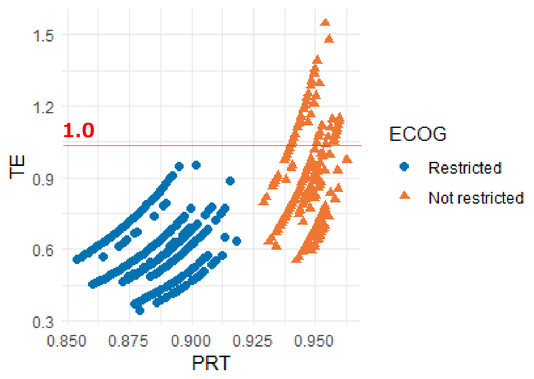
$\mathrm{TE}_i = \exp(\alpha + \boldsymbol{\gamma}^\top \boldsymbol{X}_i)$.

- Probability of receiving benefit from the treatment (*PRT*)

$\mathrm{PRT}_i = P(T_i > \tau | \boldsymbol{X}_i) = \exp(-\Lambda_0(\tau)\exp(\boldsymbol{\beta}^\top \boldsymbol{X}_i))$. ($\Lambda_0(t)$ is estimated by the Breslow estimator.)

Example

- Oak study (Rittmeyer et al., 2017): Atezolizumab vs Docetaxel in patients with previously treated non-small-cell lung cancer
  - Z : Assigned treatment (1: Atezolizumab, 0: Docetaxel)
  - X_1 : Age (standardized)
  - X_2 : Sex (1: Male, 0: Female)
  - X_3 : Smoking (1: Current, 0: Past or never)
  - X_4 : ECOG (1: Restricted, 0: Not restricted)
  - X_5 : TC/IC (1: TC1/2/3 or IC1/2/3, 0: TC0 and IC0)



Patients with ECOG = "Restricted"

- Slightly lower *PRT*
- All patients are *TE*<1.0

If surviving beyond the change-point, more likely to benefit from the treatment.

Table: Parameters estimation results

Parameter	Estimate	SE	Exp(Estimate)	95%CI
τ (Change-point)	2.431	–	–	[2.111, 4.227]
α (Treatment)	-0.169	0.259	0.845	[0.508, 1.403]
β_1 (Age)	0.083	0.057	1.087	[0.973, 1.214]
β_2 (Sex)	0.137	0.121	1.147	[0.905, 1.453]
β_3 (Smoking)	0.054	0.162	1.056	[0.769, 1.450]
β_4 (ECOG)	0.773	0.123	2.166	[1.703, 2.755]**
β_5 (TC/IC)	-0.031	0.111	0.969	[0.781, 1.204]
γ_1 (Age)	-0.124	0.086	0.883	[0.747, 1.045]
γ_2 (Sex)	0.197	0.194	1.218	[0.833, 1.781]
γ_3 (Smoking)	0.019	0.250	1.019	[0.625, 1.664]
γ_4 (ECOG)	-0.371	0.185	0.690	[0.480, 0.992]*
γ_5 (TC/IC)	-0.233	0.176	0.792	[0.561, 1.118]

$* : p < 0.05,\ ** : p < 0.001$

Reference

[1] Ozaki, R. and Ninomiya, Y. (2023). Information criteria for detecting change-points in the Cox proportional hazards model. *Biometrics*, 79, 3050–3065.

[2] Rittmeyer, A., Barlesi, F., Waterkamp, D., et al. (2017). Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. *The Lancet*, 389(10066), 255-265.

[3] Sunami, H. and Hattori, S. (2026). Semiparametric piecewise accelerated failure time model for the analysis of immune-oncology clinical trials. *Biometrics*, 82(1), ujaf171.