Bayesian analysis of restricted mean survival time adjusted on covariates using pseudo-observations

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Analysis of time-to-event outcome in randomized clinical trial

- Usually performed with a **Cox model** to provide a summary of the treatment effect
- Based on the proportional hazards (PH) assumption
- The presence of **non-PH** doubts the interpretation of a **single reported hazard ratio**
- This case of non-PH becomes more common with the development of immunotherapies[1] (delayed treatment effect)

[1] Lin et al. 2020.

Restricted Mean Survival Time (RMST)

For $\tilde{T}$ the time-to-event variable and τ a pre-specified time of interest, the τ-RMST is[2]:

$$\mathrm{RMST}(\tau) = E(\tilde{T} \wedge \tau) = \int_0^{\tau} S(t)dt$$

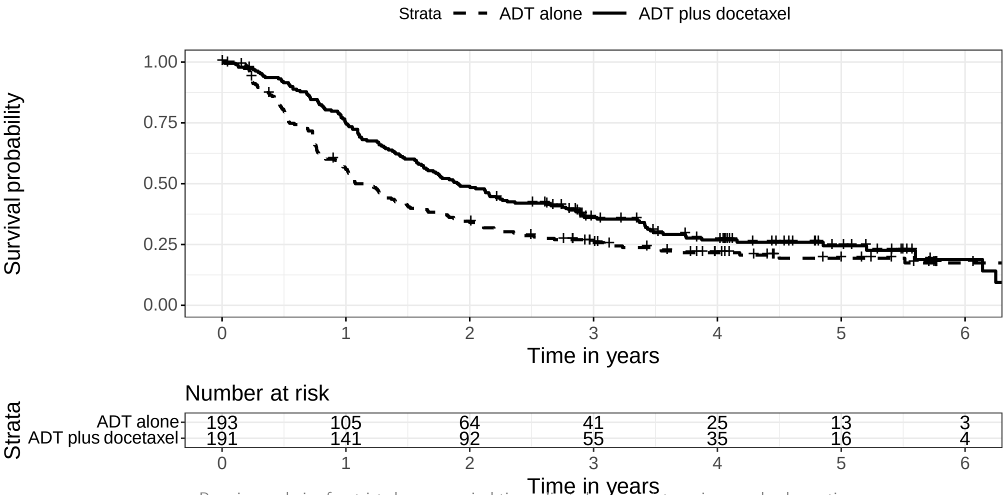
Royston and Parmar (2011) suggest using the difference in RMST (dRMST) between the two arms:

- As an **clinically meaningful** measure of the treatment effect
- The **primary measure** when non-PH is observed
- A useful **secondary measure** when the PH assumption appears to be satisfied

[2] Irwin 1949.

Real data example: Getug 15 trial

- PH assumption was rejected ($p = 0.00022$, Grambsch and Therneau test)



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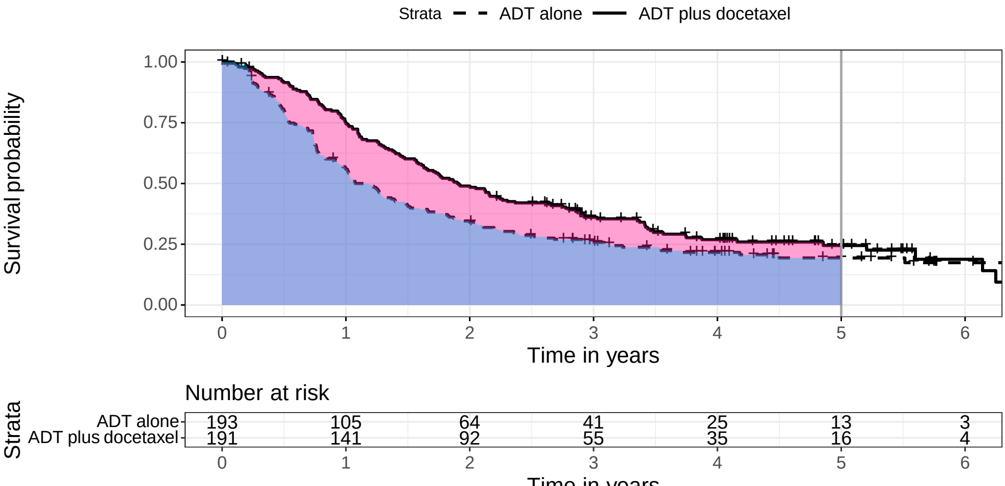

Restricted Mean Survival Time estimation

One straightforward approach to estimate RMST is to **numerically integrate the Kaplan-Meier curve** between 0 and τ

However, this approach does not allow for covariate adjustments, which is a **major limitation** because omitting important covariate results in **less precision**[3]

[3] Karrison and Kocherginsky 2018.

Frequentist methods to analyze RMST adjusted on covariates

One approach is **to model the survival function** and integrate it:

- **Piecewise exponential model** from Karrison (1987)
- **Cox model stratified on the treatment** from Zucker (1998)

↪ Both complex to implement and limited

A more natural approach is to fit a linear model **on the RMST directly**:

- Using **pseudo-observations** from Andersen et al. (2004)
- With **Inverse Probability of Censoring Weights** (IPCW) from Tian et al. (2014)

↪ Straightforward approaches

Bayesian analysis

In rare diseases or precision medicine, small sample sizes make **Bayesian methods attractive**[4]:

- Naturally suitable for including prior information (historical data borrowing)
- Provide better interpretation

With small sample sizes, it is particularly needed **to adjust the analysis on the prognostic factors** used for the randomization

[4] Lesaffre et al. 2020.

Bayesian methods to analyze RMST

Bayesian research is limited to two recent nonparametric models on the survival function:

- Zhang and Yin (2023) assign a mixture of Dirichlet processes (MDP) prior
  No covariates adjustment available
- Chen et al. (2023) overcome this limitation, with another dependent mixture model

Both methods **require to model the survival function** and are **complex to implement**

Objective

We extended the analysis of pseudo-observations in the Bayesian framework to provide a **straightforward RMST estimation adjusted on covariates**

Pseudo-observations definition

Following Andersen et al. (2004), the *i*-th pseudo-observation is computed as:

$$y_{\tau,i} = n \int_0^{\tau} \widehat{S}(t)dt - (n-1) \int_0^{\tau} \widehat{S}^{-i}(t)dt$$

where

- $\widehat{S}(t)$: Kaplan-Meier (KM) estimator at time t of survival probability
- $\widehat{S}^{-i}(t)$: KM estimator when eliminated *i*-th individual from the data set

Pseudo-observations can be interpreted as the contribution of one individual to the overall estimate.

Regression model

- Considering the following regression model **on the RMST directly**:

$$\mu_i = E(\tilde{T}_i \wedge \tau | A_i, Z_i) = \alpha + \delta A_i + \beta_1 Z_{i1} + \cdots + \beta_P Z_{iP}$$

where A is the treatment variable, $Z = (Z_1, \ldots, Z_P)^T$ other variables and $\beta = (\alpha, \delta, \beta_1, \ldots, \beta_P)^T$ the vector of unknown parameters

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- The regression coefficient, δ, can be interpreted as the dRMST between the two arms
- Assuming completely independent censoring, Overgaard et al. (2017) demonstrate **the asymptotic proprieties of pseudo-observations**

$$E(y_{\tau,i} | A_i, Z_i) \approx E(\tilde{T}_i \wedge \tau | A_i, Z_i)$$

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$\Longrightarrow$ Pseudo-observations are analyzed as an outcome of a generalized linear model

Pseudo-observations analysis

In the frequentist framework:

- Using the **Generalized Estimating Equations**[5] (GEE)
- GEE is a marginal approach that does not require specifying the full distribution
- Only (here) the first moment is specified

In the Bayesian framework:

- Using the **Bayesian Generalized Method of Moments**[6] (GMM)
- Bayesian GMM can be seen as the Bayesian counterpart of GEE
- Only the mean is specified through the use of a **pseudo-likelihood**

[5] Liang and Zeger 1986.
[6] Yin 2009.

Bayesian generalized method of moments

- A score vector is defined as

$$U_n(\beta) = \frac{1}{n}\sum_{i=1}^{n} u_i(\beta)$$

where $u_i(\beta) = \frac{\partial \mu_i}{\partial \beta}(y_{\tau,i} - \mu_i)$

- And a quadratic inference function[7] is defined using the score vector

$$Q_n(\beta) = U_n^T(\beta)\Sigma_n^{-1}(\beta)U_n(\beta)$$

with $\Sigma_n(\beta) = \frac{1}{n^2}\sum_{i=1}^{n} u_i(\beta)u_i^T(\beta) - \frac{1}{n}U_n(\beta)U_n^T(\beta)$ a $(P+2)\times(P+2)$ matrix

[7] Qu et al. 2000.

Bayesian generalized method of moments

- By the Central Limit Theorem
  - $U_n(\beta) \xrightarrow[n\to+\infty]{d} N(0, \Sigma(\beta))$, where $\Sigma(\beta) = \lim_{n\to+\infty}(\Sigma_n(\beta))$
  - $Q_n(\beta) \xrightarrow[n\to+\infty]{d} \chi^2_{P+2}$
- A chi-squared test can be defined[8], analog to the usual likelihood ratio test, where $Q_n(\beta)$ behaves like $-2\log L(y|\beta)$
- **GMM approximates the likelihood** for selected moments of the data without specifying the full likelihood[9]

[8]Hansen 1982.
[9]Chernozhukov and Hong 2003.

Bayesian generalized method of moments

- The pseudo-likelihood $\tilde{L}(\beta|y_\tau)$ is defined as

$$\begin{aligned}\tilde{L}(\beta|y_\tau) &\propto \exp\{-\frac{1}{2}Q_n(\beta)\} \\ &\propto \exp\{-\frac{1}{2}U_n^T(\beta)\Sigma_n^{-1}(\beta)U_n(\beta)\}\end{aligned}$$

- The posterior probability is estimated as

$$p(\beta|y_\tau) \propto \tilde{L}(\beta|y_\tau)p(\beta)$$

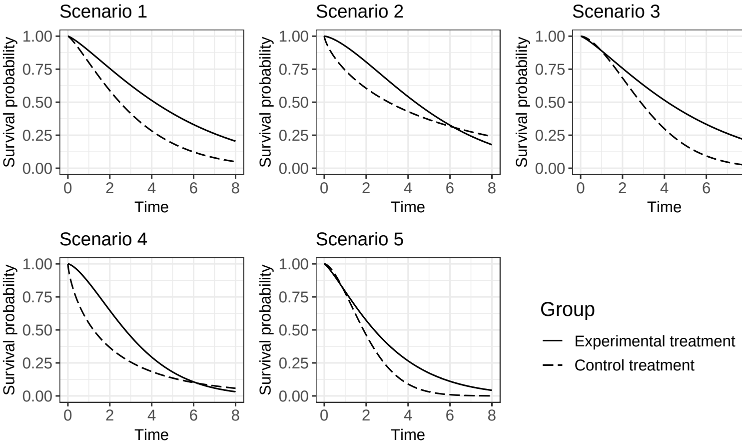
Simulation study

- Two-arm randomized clinical trials (experimental vs control)
- Event times $\sim$ Weibull distribution
- Independently,
  - Censoring times $\sim$ Uniform distribution
  - Administrative censoring at 8 years

  $\hookrightarrow \approx 30\%$ of censoring for all scenarios
- Sample sizes: $50, 100, 200, 500$
- $\tau = 5$ years

Simulation study

5 scenarios: PH (scenario 1), non-PH: early effect (scenarios 2 and 4), delayed effect (scenarios 3 and 5), with uniform covariate (scenario 4), or normal and Bernoulli covariates (scenario 5)



Simulation study

Performance metrics:

Bias, average standard error (ASE), root mean square error (RMSE), and 95% coverage rate estimated for 1000 replicates

Benchmark methods:

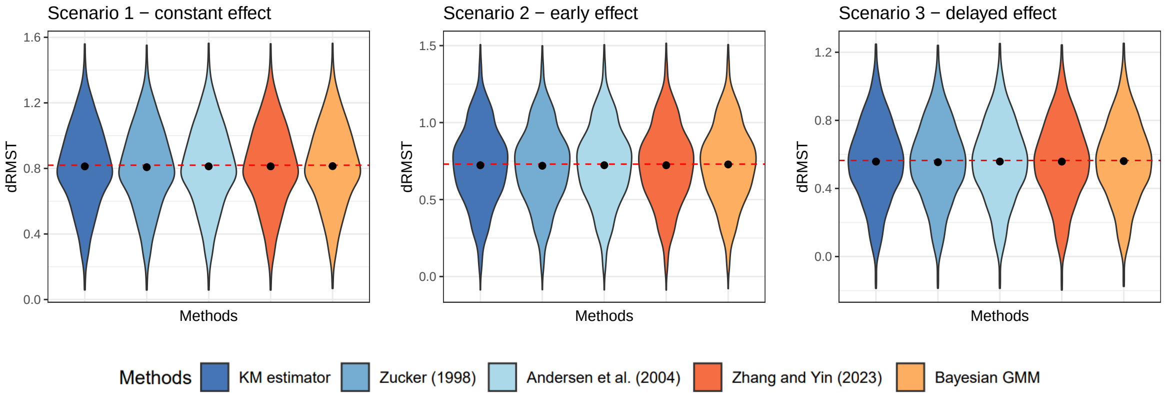
- KM estimator
- Stratified Cox model from **Zucker (1998)**
- GEE model on pseudo-observations from **Andersen et al. (2004)**
- IPCW model from **Tian et al. (2014)**
- Bayesian nonparametric model from **Zhang and Yin (2023)**

Bayesian GMM:

NUTS algorithm in Stan

- chains = 3, burn-in = 1000, iteration = 2000, priors: $\beta \sim N(\mu = 0, \sigma^2 = 10)$

Results without covariates adjustment: scenarios 1-3 ($n = 200$)



The Bayesian GMM gave valid estimations of the dRMST, with similar performances compared to the other approaches

Model misspecification: omitting prognostic variables (scenario 4: early effect)

n	Methods	Adjustment variable	Bias	ASE[1]	RMSE[2]	95% coverage rate
200	**Frequentist**					
	KM estimator	-	-0.0056	0.257	0.266	93.8
	Zucker (1998)	-	-0.0104	0.258	0.264	93.8
	Zucker (1998)	Z_1	-0.0133	0.239	0.243	93.9
	Andersen et al. (2004)	-	-0.0056	0.258	0.266	93.8
	Andersen et al. (2004)	Z_1	-0.0088	0.246	0.251	93.9
	Bayesian					
	Zhang and Yin (2023)	-	-0.0058	0.256	0.266	93.8
	GMM	-	-0.0070	0.259	0.263	94.5
	GMM	Z_1	-0.0033	0.250	0.249	94.6

[1] ASE = Average Standard Error, [2] RMSE = Root Mean Square Error

Prognostic variable $Z_1 \sim U([0, 2])$

Model misspecification: omitting prognostic variables

Other settings:

- Omitting prognostic variables also results in less precision with a delayed treatment effect (scenario 5)
- Similar results were observed for other sample sizes (n = 50, 100, 500)

Model misspecification: adding unrelated variables (scenario 4: early effect)

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	Zucker (1998)	-	-0.0104	0.258	0.264	93.8
	Zucker (1998)	Z_1	-0.0133	0.239	0.243	93.9
	Zucker (1998)	Z_1, X_1	-0.0128	0.239	0.245	93.9
	Zucker (1998)	Z_1, X_1, X_2, X_3	-0.0117	0.239	0.248	93.8
	Andersen et al. (2004)	-	-0.0056	0.258	0.266	93.8
	Andersen et al. (2004)	Z_1	-0.0088	0.246	0.251	93.9
	Andersen et al. (2004)	Z_1, X_1	-0.0074	0.246	0.251	93.9
	Andersen et al. (2004)	Z_1, X_1, X_2, X_3	-0.0068	0.246	0.254	93.7
	Bayesian					
	GMM	-	-0.0070	0.259	0.263	94.5
	GMM	Z_1	-0.0033	0.250	0.249	94.6
	GMM	Z_1, X_1	-0.0014	0.253	0.249	94.3
	GMM	Z_1, X_1, X_2, X_3	-0.0008	0.261	0.252	95.3

[1] ASE = Average Standard Error, [2] RMSE = Root Mean Square Error

Prognostic variable $Z_1 \sim U([0,2])$, other variable $X_1 \sim N(0,1)$, $X_2 \sim B(0.5)$, $X_3 \sim U([0,2])$

Model misspecification: adding unrelated variables

Other settings:

- No bias nor variance inflation was observed for the frequentist approaches with a delayed treatment effect (scenario 5)
- Similar results were observed for other sample sizes for the frequentist approaches (n = 50, 100, 500)
- Higher variance for the Bayesian GMM with n = 50 and 1-3 unrelated covariates

Application to the Getug 15 trial

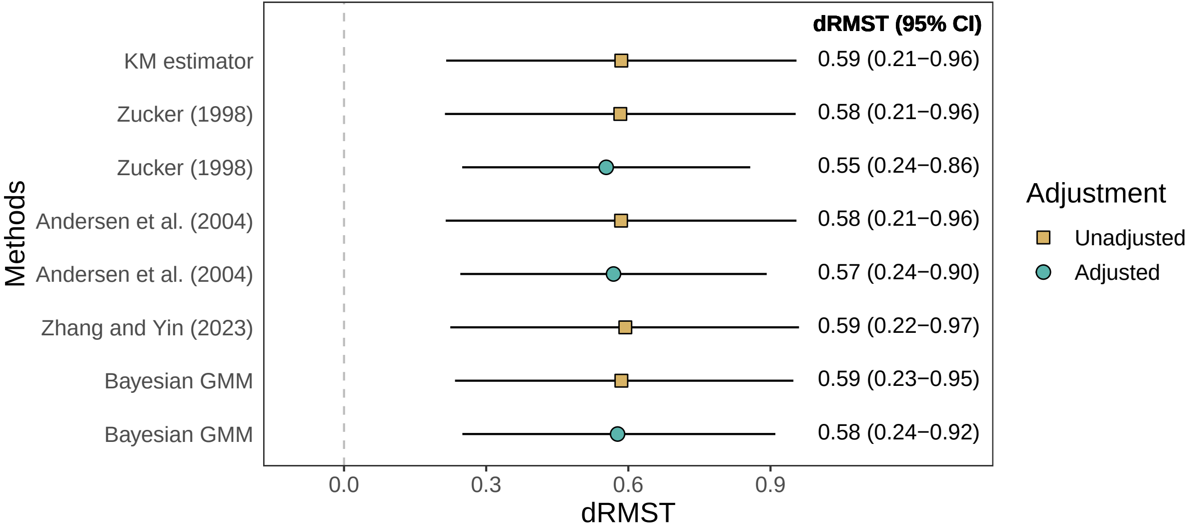
Phase 3 randomized clinical trial: comparing an androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer ($n = 384$, 25% of censoring)

Outcome of interest: Prostate-Specific Antigen (PSA) progression-free survival

Covariates adjustment:

- Gleason score (< 8 vs. ≥ 8)
- European Cooperative Oncology Group performance status (0 vs. $1 - 2$)
- Concentration of alkaline phosphatase (Normal vs. Abnormal)
- Presence of bone metastases (Yes vs. No)

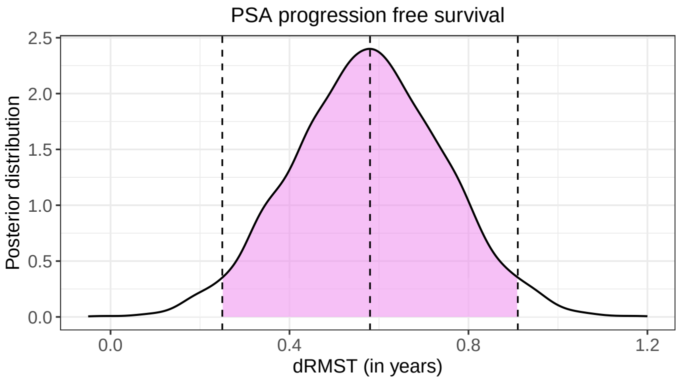
Estimation of the difference of 5-RMST between the two treatment groups



Getug 15: 5-RMST analysis with the Bayesian GMM

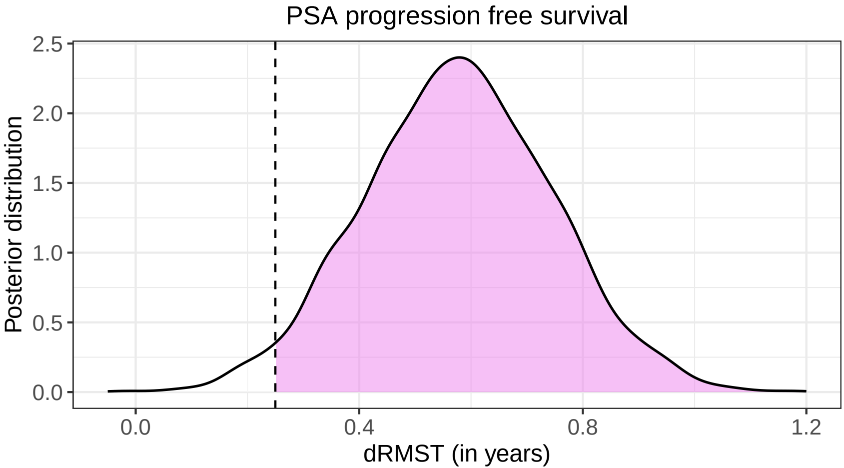
			Quantiles				
Covariate	$\widehat{\beta}$	SD	2.5%	25%	50%	75%	97.5%
Intercept	5.63	0.55	4.53	5.27	5.63	5.99	6.73
Gleason score	-0.19	0.18	-0.53	-0.30	-0.19	-0.07	0.15
ECOG performance status	-0.55	0.18	-0.90	-0.68	-0.56	-0.44	-0.21
Alkaline phosphatase concentration	-1.25	0.18	-1.60	-1.37	-1.24	-1.12	-0.89
Presence of bone metastases	-0.49	0.27	-1.01	-0.68	-0.49	-0.31	0.04
Treatment	0.58	0.17	0.25	0.46	0.58	0.69	0.91

Getug 15: Estimation of the difference of 5-RMST with the Bayesian GMM



- The mean of the posterior samples is 0.58 year (95% credible interval: 0.24-0.92). On average, receiving docetaxel in addition to ADT increases the lifetime without PSA progression during the next 5 years by 0.58 year compared to receiving ADT alone.

Getug 15: Estimation of the difference of 5-RMST with the Bayesian GMM



- $\mathrm{P}(\mathrm{dRMST}(5) \geq 3$ months $) = 0.97$

Discussion

We propose a **Bayesian** approach for analyzing RMST **adjusted on covariates**:

- Combining the flexibility of **pseudo-observations**:
  - To fit a straightforward linear model, without specifying any model on the survival function
  - To estimate not only the treatment effect but also the covariate effects
- With **the Bayesian GMM:**
  - To allow for including prior information in the analysis
  - To benefit from the advantages of the Bayesian interpretation

Perspectives:

- Extend this approach to the joint analysis of RMST at multiple time points

References i

- Andersen, Per Kragh et al. (2004). **"Regression Analysis of Restricted Mean Survival Time Based on Pseudo-Observations".** In: *Lifetime Data Analysis* 10.4, pp. 335–350. ISSN: 1380-7870, 1572-9249. DOI: *10.1007/s10985-004-4771-0*.
- Chen, Ruizhe et al. (2023). ***Restricted Mean Survival Time Estimation Using Bayesian Nonparametric Dependent Mixture Models.*** arXiv: *2305.14639 [stat]*. URL: *http://arxiv.org/abs/2305.14639* (visited on 12/07/2023). preprint.
- Chernozhukov, Victor and Han Hong (Aug. 1, 2003). **"An MCMC Approach to Classical Estimation".** In: *Journal of Econometrics* 115.2, pp. 293–346. DOI: *10.1016/S0304-4076(03)00100-3*.
- Hansen, Lars Peter (July 1982). **"Large Sample Properties of Generalized Method of Moments Estimators".** In: *Econometrica* 50.4, pp. 1029–1054. DOI: *10.2307/1912775*. JSTOR: *1912775*.

- Irwin, J. O. (1949). **"The Standard Error of an Estimate of Expectation of Life, with Special Reference to Expectation of Tumourless Life in Experiments with Mice".** In: *The Journal of Hygiene* 47.2, pp. 188–189. ISSN: 0022-1724. pmid: *15406758*. URL: *https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2234920/* (visited on 05/14/2024).
- Karrison, Theodore (1987). **"Restricted Mean Life With Adjustment for Covariates".** In: *Journal of the American Statistical Association* 82.400, pp. 1169–1176. ISSN: 0162-1459. DOI: *10.2307/2289396*. JSTOR: *2289396*.
- — (1997). **"Use of Irwin's Restricted Mean as an Index for Comparing Survival in Different Treatment Groups—Interpretation and Power Considerations".** In: *Controlled Clinical Trials* 18.2, pp. 151–167. ISSN: 0197-2456. DOI: *10.1016/S0197-2456(96)00089-X*.

- Karrison, Theodore and Masha Kocherginsky (2018). **"Restricted Mean Survival Time: Does Covariate Adjustment Improve Precision in Randomized Clinical Trials?"** In: *Clinical Trials* 15.2, pp. 178–188. ISSN: 1740-7745, 1740-7753. DOI: *10.1177/1740774518759281*.
- Lesaffre, Emmanuel et al., eds. (2020). ***Bayesian Methods in Pharmaceutical Research.*** New York: Chapman and Hall/CRC. 546 pp. ISBN: 978-1-315-18021-2. DOI: *10.1201/9781315180212*.
- Liang, Kung-Yee and Scott Zeger (1986). **"Longitudinal Data Analysis Using Generalized Linear Models".** In: *Biometrika* 73.1, pp. 13–22. ISSN: 0006-3444. DOI: *10.1093/biomet/73.1.13*.
- Lin, Ray S. et al. (Apr. 2, 2020). **"Alternative Analysis Methods for Time to Event Endpoints Under Nonproportional Hazards: A Comparative Analysis".** In: *Statistics in Biopharmaceutical Research* 12.2, pp. 187–198. ISSN: null. DOI: *10.1080/19466315.2019.1697738*.

- Overgaard, Morten et al. (2017). **"Asymptotic Theory of Generalized Estimating Equations Based on Jack-Knife Pseudo-Observations".** In: *The Annals of Statistics* 45.5, pp. 1988–2015. ISSN: 0090-5364, 2168-8966. DOI: *10.1214/16-AOS1516*.
- Qu, Annie et al. (Dec. 1, 2000). **"Improving Generalised Estimating Equations Using Quadratic Inference Functions".** In: *Biometrika* 87.4, pp. 823–836. DOI: *10.1093/biomet/87.4.823*.
- Royston, Patrick and Mahesh K. B. Parmar (2011). **"The Use of Restricted Mean Survival Time to Estimate the Treatment Effect in Randomized Clinical Trials When the Proportional Hazards Assumption Is in Doubt".** In: *Statistics in Medicine* 30.19, pp. 2409–2421. ISSN: 02776715. DOI: *10.1002/sim.4274*.
- Tian, Lu et al. (2014). **"Predicting the Restricted Mean Event Time with the Subject's Baseline Covariates in Survival Analysis".** In: *Biostatistics (Oxford, England)* 15.2, pp. 222–233. ISSN: 1465-4644. DOI: *10.1093/biostatistics/kxt050*. pmid: *24292992*.

- Yin, Guosheng (2009). **"Bayesian Generalized Method of Moments".** In: *Bayesian Analysis* 4.2, pp. 191–208. ISSN: 1936-0975. DOI: *10.1214/09-BA407*.
- Zhang, Chenyang and Guosheng Yin (2023). **"Bayesian Nonparametric Analysis of Restricted Mean Survival Time".** In: *Biometrics* 79.2, pp. 1383–1396. ISSN: 1541-0420. DOI: *10.1111/biom.13622*. pmid: *35034347*.
- Zucker, David M. (1998). **"Restricted Mean Life with Covariates: Modification and Extension of a Useful Survival Analysis Method".** In: *Journal of the American Statistical Association* 93.442, pp. 702–709. ISSN: 0162-1459. DOI: *10.2307/2670120*. JSTOR: *2670120*.

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