



# Efficient Estimation of Survival Prognosis Under Immortal Time Bias

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## OVERVIEW & MOTIVATIONS

1. We consider the problem of efficiently estimating survival prognosis under a data structure complicated by the presence of immortal time bias.
2. The matter of efficient estimation under a bias induced by time-dependent risks presents a novel challenge that received surprisingly meager attention in the literature.
3. We compare parametric and nonparametric estimators of survival, including variations of the Cox proportional hazards model and the Kaplan-Meier estimator, evaluating the efficiency of each in the estimation of the multiple survival processes that occur under this data-generating process.
4. We are given survival times for patients with a single primary melanoma, and some of the patients develop a second primary melanoma before dying.

## INTRODUCTION & DATA

- Question of interest: **How does the second melanoma change the survival prognosis of the patients?**
- In order to prepare for a real data analysis, we simulate a data structure that matches what we expect — that is, the data-generating process is the the Cox proportional hazards model.
- Survival time  $T$ : time before the actual death of the patient,
- Time until second melanoma appears:  $U$ ,
- Baseline hazard in absence of second melanoma:  $\lambda_0(t)$ ,
- Time-varying covariate:  $Z(t) = I(t > U)$ .
- Constant baseline hazard  $\lambda_0 = \lambda$ .
- A second melanoma doubles the hazard.

## METHODOLOGY II

- The second approach is non-parametric and uses Kaplan-Meier's estimator defined as

$$\hat{S}(t) = \prod_{i:t^{(i)} < t} \left(1 - \frac{d_i}{n_i}\right), \quad t \geq 0,$$

where  $d_i$  and  $n_i$  are the respective numbers of death and individual at risks at the ordered time  $t^{(i)}$ ,  $i = 1, \dots, n$ .

- Youlden et al. [1] only uses patients for whom no occurrence of a second melanoma is observed, in the estimation of  $S_1$  and ignores the other patients, which causes a bias.
- Jewell corrects their estimator by including all the patients in the study.
- The ones that were excluded by Youlden et al. [1] still contain information about  $\lambda_1$ : those are censored observations at time  $U$ .

## METHODOLOGY I

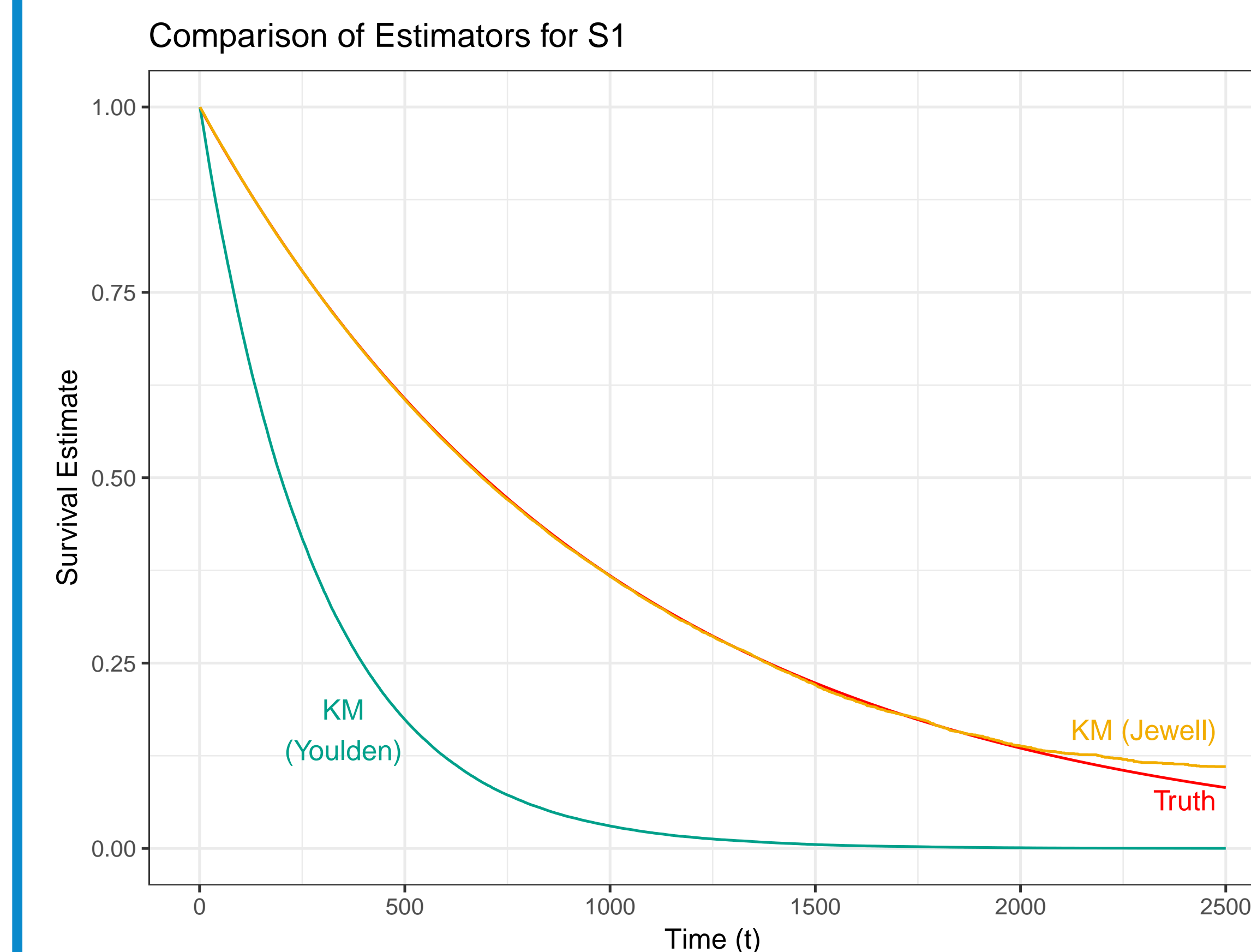
- Time origin for all subjects: date of their first or index primary melanoma (PM).
- Two hazard functions of essential interest:
- $\lambda_1(t)$  — hazard of an individual, alive at time  $t$  who has only experienced one PM.
- $\lambda_2(t)$  — hazard of an individual, alive at time  $t$  who has experienced more than one PM.
- Data: of  $n = n_1 + n_2$  subjects.
- The first  $n_1$  only experience one PM before death at the observed time  $t_i$ . The other  $n_2$  experience a second PM at the observed time  $u_j$  and then die at observed time  $t_j$ . It is possible to consider censored observations for both sets of subjects but we do not discuss this here for the sake of notation.
- We compare three approaches of this problem, namely, the Cox proportional hazards model, the method presented in Youlden et al. [1] and its correction by Jewell.

The basic proportional hazards model is a semi-parametric model for the hazard function defined by

$$\lambda(t; Z = z) = \lambda_0(t) \exp(\beta^T z), \quad t \geq 0. \quad (1)$$

where  $\lambda_0(\cdot)$  is the baseline hazard function is estimated non-parametrically, while  $\beta$  is the vector of regression coefficients and is estimated parametrically using Cox's partial likelihood.

## RESULTS & DISCUSSION



**Figure 1:** Average performance of estimators for  $S_1$  for a sample of size  $n = 1000$ , over about 300 simulations.

- The Kaplan-Meier estimator proposed by Youlden displays obvious bias.
- The estimates of the survival curve produced by Cox regression and the Kaplan-Meier estimator with the Jewell correction show no such bias.
- Under the Cox model, Cox regression will outperform other estimators — it draws upon information across both subject groups over all time points.
- The Kaplan-Meier estimator exhibits a slight divergence from the truth in the right tail due to a well-studied finite-sample bias caused by censored observations.
- We display results for  $n = 1000$  since this sample size is closest to that from the observational medical study we analyze.

## PRINCIPAL REFERENCES

- [1] Danny R Youlden, Peter D Baade, H Peter Soyer, Philippa H Youl, Michael G Kimlin, Joanne F Aitken, Adele C Green, and Kiarash Khosrotehrani. Ten-year survival after multiple invasive melanomas is worse than after a single melanoma: a population-based study. *Journal of Investigative Dermatology*, 136(11):2270–2276, 2016.
- [2] Wei-Yann Tsai, Nicholas P Jewell, and Mei-Cheng Wang. A note on the product-limit estimator under right censoring and left truncation. *Biometrika*, 74(4):883–886, 1987.
- [3] Steven M Snapinn, Qi Jiang, and Boris Iglewicz. Illustrating the impact of a time-varying covariate with an extended kaplan-meier estimator. *The American Statistician*, 59(4):301–307, 2005.

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