Mean survival time by ordered fractions of population with censored data

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Mean survival by ordered fractions

- Let T be a non-negative random variable with $\mathrm{E}[T] < \infty$.
- Expectation of T can be expressed as

$$\mu = \mathrm{E}[T] = \int_0^\infty S(t)\mathrm{d}t = \int_0^1 Q(p)\mathrm{d}p, \tag{1}$$

where $S(\cdot)$ and $Q(\cdot)$ denote the survival and quantile functions, respectively.

- Given $\{\lambda_0, \lambda_1, \ldots, \lambda_K\}$ grid of proportions, we divide μ into separate components

$$\mu = \sum_{k=1}^{K} \mu_k, \text{ where } \mu_k = \int_{\lambda_{k-1}}^{\lambda_k} Q(p)\mathrm{d}p, \quad \lambda_0 = 0 \text{ and } \lambda_K = 1, \tag{2}$$

with $\lambda_{k-1} < \lambda_k, \forall k \in \{1, \ldots, K\}$.

- Weighting each μ_k by its corresponding inverse proportion

$$\overline{\mu}_k = \frac{\mu_k}{\lambda_k - \lambda_{k-1}},$$

we obtain the mean survival time for the fraction of population defined by $(\lambda_{k-1}, \lambda_k)$.

Easy interpretation

If $(\lambda_0, \lambda_1) = (0, 0.5)$, $\overline{\mu}_1$ quantifies mean survival time for the first half of the population to experience the event of interest.

- In the presence of a censoring variable C, when $Y = \min(T, C)$ is observed, λ_K in (2) can be set to the largest proportion of observed events (corresponding to the last observed quantile).

Estimation and simulation results

- We estimate μ_k via the Kaplan-Meier estimator of the underlying survival function.
- Given $\widehat{S}(\cdot)$ and the grid of proportions $\{\gamma_0, \gamma_1, \ldots, \gamma_K\} = \{1-\lambda_0, 1-\lambda_1, \ldots, 1-\lambda_K\}$, from (1) and (2)

$$\begin{aligned}\widehat{\mu_k} &= \sum_{j=1}^{J_k} y_j[\min\{\widehat{S}(y_{j-1}), \gamma_{k-1}\} - \max\{\widehat{S}(y_j), \gamma_k\}] \\ &= \sum_{j_k=1}^{J_k} \widehat{Q}(p_j)(p_j - p_{j-1}),\end{aligned}$$

where y_j are observed event times such that $\widehat{S}(y_j) \in [\gamma_k, \gamma_{k-1}], \forall j \in \{1, \ldots, J_k\}$, and $\widehat{S}(y_0) \geq \gamma_{k-1}$ and $\widehat{S}(y_{J_k}) \leq \gamma_k$.

Table 1: Average over 5,000 samples with 200 observations from a log-logistic model with scale $\alpha = 1$ and shape $\beta = 2$, and censoring variable uniform in $(0, 7/3)$ (average censoring rate of 50%).

k	λ_k	μ_k	$\widehat{\mu_k}$	$\widehat{\mu_k^L} - \widehat{\mu_k^U}$	nsim$_k$	d$_k$
1	0.20	0.064	0.064	0.044 − 0.086	100%	34
2	0.40	0.131	0.132	0.101 − 0.175	100%	29
3	0.60	0.201	0.202	0.156 − 0.264*	100%	23
4	0.80	0.311	0.304	0.226 − ∞	70.7%	14
5	0.95	0.420	0.307	0.239 − ∞	5.80%	4

Where

- μ_k true mean survival time for fraction $(\lambda_{k-1}, \lambda_k)$.
- $\widehat{\mu_k}$ estimated mean survival time for fraction $(\lambda_{k-1}, \lambda_k)$.
- $\widehat{\mu_k^L}$ and $\widehat{\mu_k^U}$ lower and upper bounds integrating over equal precision confidence bands for the Kaplan-Meier estimator [1].
- nsim$_k$ % of simulations where $\widehat{\mu_k}$ could be computed.
- d$_k$ number of observed events.

Precision

Estimates' precision decreases with increasing k, as the proportion of censored observations increases with k and, on average, fewer events are observed.

Mean survival by ordered fractions vs. Restricted mean

When $\lambda_K < 1$, the mean survival time for the λ_K-th fraction of the population observed to experience the event, does not correspond to the restricted mean [2] computed up to the last observed quantile $y^\star = Q(\lambda_K)$, i.e.,

$$\overline{\mu}_K = \frac{1}{\lambda_K}\int_0^{\lambda_K} Q(p)\mathrm{d}p \neq \int_0^{y^\star} S(y)\mathrm{d}y = \mu^\star.$$

Application example: Survival after bone marrow transplant in lymphoma patients

- Data on 35 patients with lymphoma that received either an allogenic or an autologous bone marrow transplant [3].
- Aim of the study: finding differences in lymphoma-free survival after having received either type of transplant.

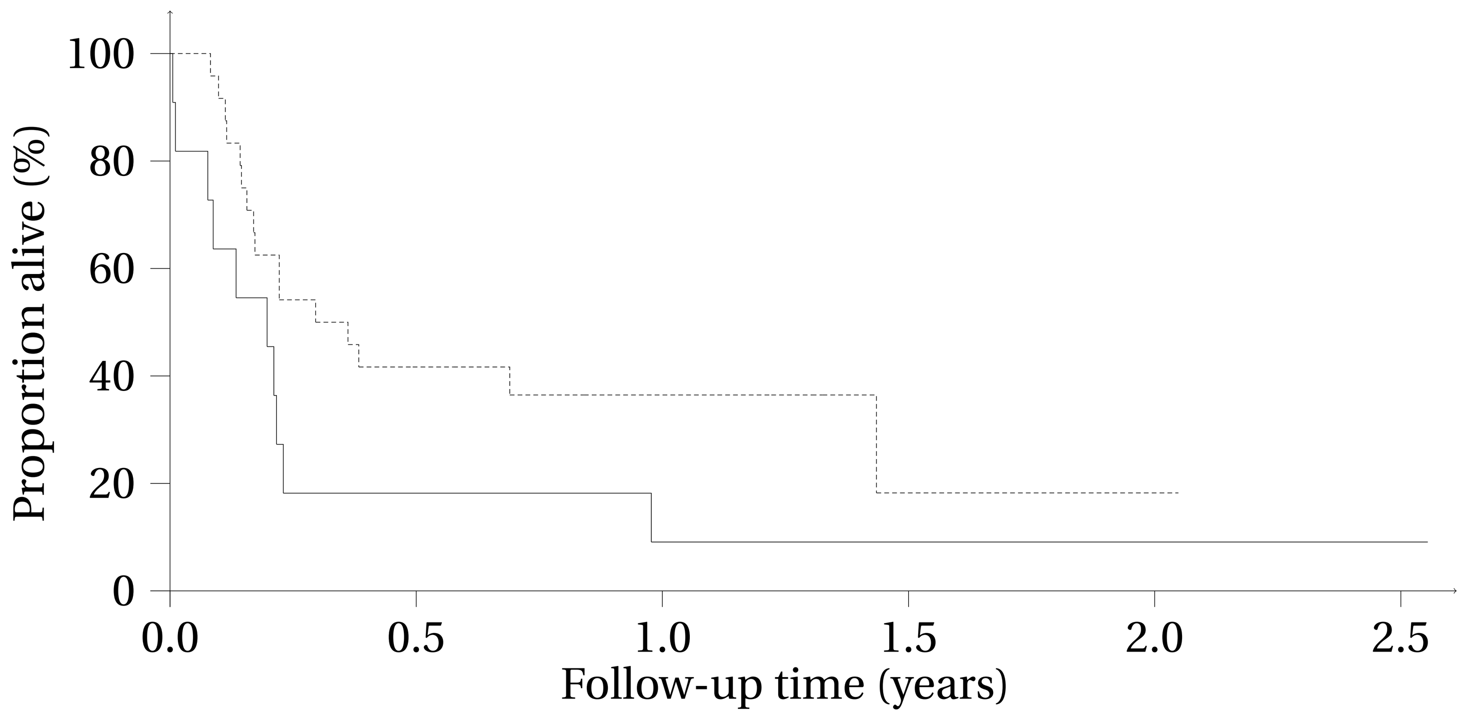

Figure 1: Estimated Kaplan-Meier survival curves after bone marrow transplant for lymphoma patients that received allogenic (solid line) or autologus (dashed line) transplant.

Results' comparison

- Restricted mean survival estimates do not detect significant differences between groups

146.5 days, 95% CI $(-29.71, 322.7)$.

- Mean survival by ordered fractions estimates detect significant differences among earlier failures

32.15 days, 95% CI $(13.98, 50.31)$,

among the weakest 10% of the patients (first 10% to die or relapse in each group after receiving the transplant).

Table 2: Estimates for mean survival differences (in days) between allogenic $(\widehat{\mu^0}_k)$ and autologous $(\widehat{\mu^1}_k)$ bone marrow transplants with bootstrapped 95% confidence intervals by ordered deciles of population up to the last commonly observed fraction (80th percentile).

k	λ_k	$\widehat{\mu^1}_k - \widehat{\mu^0}_k$	95% CI
1	0.1	32.15	13.98 − 50.31
2	0.2	36.72	2.843 − 70.60
3	0.3	26.23	−19.94 − 72.43
4	0.4	28.98	−40.51 − 98.48
5	0.5	32.80	−124.5 − 190.1
6	0.6	80.60	−1283 − 1444
7	0.7	349.4	−446.4 − 1145
8	0.8	441.4	−130.3 − 1013

- We detected an improvement on lymphoma-free survival for the autologus transplant group amongst the weakest 20% of patients, that is, amongst those who first died or relapsed.
- No difference between the groups was detected when using restricted mean estimates.

References

[1] Nair, V.N. Confidence Bands for Survival Functions with Censored Data: A Comparative Study *Technometrics*, 26(3):265-275, 1984.

[2] Irwin, J. O. The Standard Error of an Estimate of Expectation of Life, with Special Reference to Expectation of Tumourless Life in Experiments with Mice. *Journal of Hygiene* 47(2):188-189, 1949.

[3] Avalos, B.R., Klein, J.L., Kapoor, N., Tutschka, P.J., et al. Preparation for Marrow Transplantation in Hodgkin's and non-Hodgkin's Lymphoma Using Bu/CY. *Bone Marrow Transplantation* 12(2):133-138, 1993.

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