Sample size calculation based on differences of quantiles from censored data

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Objectives

- We present a method for computing the **minimum sample size** required to detect a significant treatment effect using differences in quantiles of survival time in the presence of nonproportional hazards.
- We propose a new procedure for **density estimation** adapted to our problem.

Introduction

- In randomized clinical trials we deal with **right-censored** data: we are interested in $\tilde{T}$ but we observe $T = \tilde{T} \wedge C$ for a censoring time C.
- Standard methods exist to determine the **sample size** when the estimand is a hazard ratio in the presence of censoring, but they impose the hazard ratio of two treatments to be proportional.
- **Comparing cancer treatments:** immunotherapy's mechanism is indirect, resulting in delayed treatment effects $\Rightarrow$ Nonproportional hazards!

Method

- Test of equality of quantiles of survival time as proposed in Kosorok[2]:
  - ↪ The p^{th} **quantile of survival time** $\tilde{T}$ with cumulative distribution function F is $F^{-1}(p) = \inf_p\{P(\tilde{T} \leq t) \geq p\}$
1. Allows for quantile-varying treatment effects;
2. Accomodates for nonproportional hazards;
3. Is clinically interpretable as a function of time.

Univariate test for equality of quantiles

For distribution functions F, G and some probability p, we are interested in testing, for a fixed difference Δ:

$$H_0 : F^{-1}(p) = G^{-1}(p) \text{ vs. } H_1 : F^{-1}(p) - G^{-1}(p) = \Delta$$

We denote as n_1, n_2 the sample sizes in groups 1 and 2, and define $\mu \in (0, 1)$ such that $\frac{n_1}{n} \to \mu$ as $n \to \infty$.
Let $H(t) = P(\tilde{T} \wedge C > t)$ be the survival function of the observed time and $\Lambda(t)$ be the cumulative hazard function for $\tilde{T}$.
Then the **asymptotic distribution of the test statistic** ξ_n **under** H_0 is:

$$\xi_n = \sqrt{n}\frac{\hat{F}^{-1}(p) - \hat{G}^{-1}(p)}{\hat{\sigma}_{H0}} \xrightarrow{d} \mathcal{N}(0, 1) \text{ as } n \to \infty$$

where:

$$\hat{\sigma}^2_{H0} = \frac{\hat{\phi}}{\hat{\mu}\hat{f}(\hat{F}^{-1}(p))^2} + \frac{\hat{\gamma}}{(1-\hat{\mu})\hat{g}(\hat{G}^{-1}(p))^2}$$

$$\hat{\phi} = (1-p)^2 \int_0^{\hat{F}^{-1}(p)} \frac{d\hat{\Lambda}(x)}{\hat{H}(x)}, \qquad \hat{\gamma} = (1-p)^2 \int_0^{\hat{G}^{-1}(p)} \frac{d\hat{\Lambda}(x)}{\hat{H}(x)}$$

The **power** of the test of level α is given by:

$$1 - \beta = 1 - \Phi\left(q_{1-\alpha/2} - \frac{\sqrt{n}}{\hat{\sigma}_{H0}}\Delta\right) + \Phi\left(-q_{1-\alpha/2} - \frac{\sqrt{n}}{\hat{\sigma}_{H0}}\Delta\right)$$

where $q_{1-\alpha/2}$ denotes the quantile of order $1 - \alpha/2$ of the standard normal distribution and Φ its cumulative distribution function.

Multivariate test of equality of quantiles

We may test multiple quantiles at the same time:

$$H_0 : F^{-1}(p_j) = G^{-1}(p_j), j = 1, ..., J \text{ vs. } H_1 : \exists i \in \{1, ..., J\}, F^{-1}(p_i) \neq G^{-1}(p_i)$$

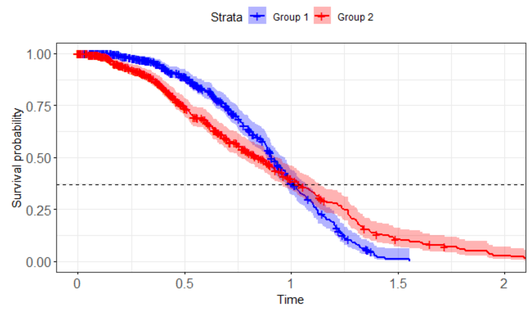
We may define $\Psi \in \mathbb{R}^{J \times J}$ such that, under H_0:

$$Z_n = \sqrt{n}\begin{bmatrix} \hat{F}^{-1}(p_1) - \hat{G}^{-1}(p_1) \\ \vdots \\ \hat{F}^{-1}(p_J) - \hat{G}^{-1}(p_J) \end{bmatrix} \xrightarrow{d} \mathcal{N}(0, \Psi) \text{ as } n \to \infty$$

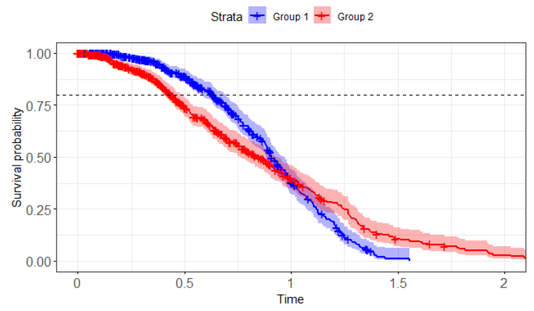
Then we have the test statistic $\xi_n = Z_n^T \Psi^{-1} Z_n$, which follows asymptotically χ^2_J under H_0.

Simulation results for the univariate test

Weibull survival times with 20% of censored observations:



Under H_0: p-value of 0.66



Under H_1: p-value of $4.4e^{-8}$

Density estimation at the quantiles

- **Drawback** of the Kosorok method: requires density estimation at the quantiles.
- The author proposes the use of kernel density estimators which:

1. Requires a **bandwidth parameter**;
2. Has a **nonparametric** estimation convergence rate.

Our proposal for density estimation

Let $Z \sim \mathcal{N}(0, 1)$ and define $\tilde{F}^{-1}(p) = \hat{F}^{-1}(p) + \frac{Z}{\sqrt{n}}$.
We propose a **least squares resampling** procedure to estimate $f(F^{-1}(p))$, for ϵ a gaussian error term:

$$\underbrace{\sqrt{n}(\hat{F}(\tilde{F}^{-1}(p)) - p)}_{\vec{Y}} = -f(F^{-1}(p))\vec{Z} + \vec{\epsilon}$$

LS resampling:

1. Generate B realizations of the centered normal, denoted by $Z_1, ..., Z_B$;
2. Calculate $y_b := \sqrt{n}\left(\hat{F}\left(\hat{F}^{-1}(p) + \frac{Z_b}{\sqrt{n}}\right) - p\right), b = 1, ..., B$;
3. Estimate $f(F^{-1}(p))$ by least squares: $\hat{f}(F^{-1}(p)) = (Z'Z)^{-1}Z'Y$

Results

- We compare two estimations of the density at the quantile of order 0.5 based on 500 replications. Data follows an **Exponential** distribution with 25% of censored observations, with group sample sizes of 500.
- The **true** density at the median is equal to 0.75.
- For the **resampling** procedure proposed, we generate B centered normal variables with standard deviation SD.
- The **kernel density estimator** uses a gaussian kernel with bandwidth parameter BW.

	Estimation	B	SD	BW	Bias	Variance	MSE
LS	0.776	1000	1		-0.026	0.173	0.174
	0.768	1000	2		-0.018	0.177	0.178
	0.787	10000	1		-0.037	0.167	0.168
	0.771	10000	2		-0.021	0.176	0.177
KDE	0.756			0.1	-0.006	0.184	0.184
	0.345			1	0.404	0.226	0.389

Conclusions

- We developed expressions for test statistics and **power** of test that allows to estimate **sample size** in the presence of nonproportional hazards.
- We propose a procedure for **density estimation** which:
  1. Requires **no smoothing parameter**;
  2. Has a **parametric** convergence rate.

References

[1] Eaton, A., Therneau, T., Le-Rademacher, J. (2020), *Designing clinical trials with (restricted) mean survival time endpoint: practical considerations*, Clinical Trials.

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[3] Lin, C., Zhang, L., & Zhou, Y. (2015), *Conditional quantile residual lifetime models for right censored data*, Lifetime data analysis.

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