Univariate and multivariate tests of equality of quantiles with right-censored data

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Abstract

A nonparametric test for equality of quantiles in the presence of right-censored data is studied. We propose to construct an asymptotic test statistic for the comparison of one quantile between two treatment groups, as well as for the comparison of a collection of quantiles. Under the null hypothesis of equality of quantiles, the test statistic follows asymptotically a normal distribution in the univariate case and a χ^2 with J degrees of freedom in the multivariate case, with J the number of quantiles compared. Deriving the variance of the test statistic requires the estimation of the probability density function of the distribution of failure times at the quantile being tested. A resampling method is presented as an alternative to kernel density estimation to perform such task. Extensive simulation studies are performed to show that the proposed approach provides reasonable type I probabilities and powers. We illustrate the proposed test in a phase III randomized clinical trial where the proportional hazards assumption between treatment arms does not hold.

Keywords

Censored data, Nonparametric methods, Clinical trial design, Nonproportional hazards, Sample size, Power

1 Introduction

In clinical studies with right-censored data, investigators have been increasingly interested in estimating the quantiles of the survival times, which are defined as being the smallest time when survival exceeds a threshold of interest [1,2]. As this measure is expressed in the timescale, the quantification of the benefit of one treatment arm over the other can be easily communicated and understood by clinicians and patients,

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in contrast to relative risk measures such as the hazard ratio which can be easily misinterpreted[3,4]. In addition to allowing the benefit, if any, of the new treatment to be expressed in terms of time gained compared to the standard of care, the use of quantiles allows for robustness against outliers and does not depend on the shape of the survival distribution or the proportionality of the treatment effect. In particular, in immuno-oncology trials the usual assumption of proportional hazards between treatment arms is often not verified due to the delayed effect of immunotherapy and late separation of survival curves[1]. Given that the quantification of treatment effects using differences in quantiles inherently accounts for nonproportional hazards, this approach is particularly well-suited for such scenarios.

Few methods have been developed to compare quantiles of the survival function in the presence of censored data. Brookmeyer and Crowley (BC)[5] proposed a pooled-weighted Kaplan-Meier estimation approach in order to detect differences in the median survival times among several treatments. In order to avoid the estimation of the densities of the time-to-event in each treatment group, the authors proposed a simplified test statistic, which is only valid under the assumption that the survival distributions are equal in each group under the null hypothesis. However, testing for homogeneity of survival distributions is much stronger than testing for equality of survival medians. Indeed, identical survival distributions imply equal median survival times, while the converse is not true. Therefore, type I error is inflated when distributions differ between treatment groups for this method, which makes its application to real data limited.

The BC test was modified by Tang and Jeong[6], who employed contingency tables as an alternative to calculating the inverse of the BC test statistic in order to avoid estimating the density distribution of failure times. Rahbar et al.[7] proposed another nonparametric test, similar to the BC test, but where the difficulty of estimating the density is addressed by using the bootstrap approach to obtain the asymptotic variance of the test. In general these nonparametric methods have inflated type I error rates, which make their use limited in practice, especially when the sample sizes are small[8]. Another extension of the BC test has been proposed by Chen and Zhang[8]. However, like all aforementioned methods, this test can only be applied to compare one quantile at a time and authors do not propose an explicit calculation of the power of the test. Moreover, these previous works do not address the formulation of clinical trials, which is a key aspect in the context of sample size estimation and in analyzing the impact of design parameters on the power of the test.

A versatile method for evaluating treatment effects by comparing pre-specified quantiles in each treatment group was proposed by Kosorok[9]. The author derived a nonparametric two-sample test for the comparison of quantiles that allows for testing the equality of multiple quantiles as well as testing the equality of one single quantile obtained at multiple analysis times. The test also applies to general censoring schemes, such as double censoring for instance, and several kinds of empirical distribution estimators. It can also be directly applied to group sequential clinical designs with staggered patient entry.

However, the estimation of the variance of the test statistic depends on the value of the density of survival at the quantile of interest. Kosorok proposed the use of kernel density estimators in order to complete this task. A drawback of this approach is that it requires the estimation of the density at all points and relies on an unknown bandwidth parameter, which has an impact on the estimator's performance[10]. To address this issue, we propose a resampling approach inspired by Lin et al.[11] to estimate the density directly at the point of interest without requiring a bandwidth parameter. We compare the Type I error

and the power obtained using both density estimation methods for testing the equality of quantiles in the presence of data and observe an improved performance of our method.

Under Kosorok's framework, the key contribution of our work is the explicit derivation of closed-form formulas for the asymptotic power of the test for both univariate and multivariate quantile comparisons. This method is illustrated in clinical trial planning and minimal sample size calculation, as well as in testing for the equality of quantiles in the presence of clinical trial data.

This paper is organized as follows. First, we present the theoretical results for the univariate and multivariate tests of equality of quantiles. Next, we derive analytical power of the test in the context of planning clinical trials with known survival distributions. We then present applications of the method to a lung cancer dataset from the OAK randomized clinical trial [12], where we illustrate its use in comparing both single and multiple quantiles. We conclude with a discussion.

2 Methods

We consider a two-arms clinical trial, where n_1 patients are randomly allocated to treatment group 1 and n_2 to treatment group 2. We observe for each patient $i \in \{1, ..., n_k\}$, $k = 1, 2$, the observed times $T_{ik} = \min(\tilde{T}_{ik}, C_{ik})$ and censoring status $\delta_{ik} = \mathbb{1}_{\tilde{T}_{ik} \leq C_{ik}}$, where $\tilde{T}_{ik}$ are the continuous times of interest and $\tilde{C}_{ik}$ the censoring times. Let $n = n_1 + n_2$ and $\hat{\mu}_k = n_k/n$, we assume that $\hat{\mu}_k$ converges to an element μ_k in $(0, 1)$. We also assume that the event times $\tilde{T}_{1k}, \ldots, \tilde{T}_{n_k k}$ and the censoring times $C_{1k}, \ldots, C_{n_k k}$ are independent, for $k = 1, 2$. Let F_k be the cumulative distribution function in each treatment arm with f_k, Λ_k and S_k the density, hazard, cumulative hazard and survival functions, respectively. We denote the survival function of the observed times T_{ik}, as H_k. We define the usual inverse distributions as $F_k^{-1}(p) = \inf\{t : F_k(t) \geq p\}$, $k = 1, 2$, for a given probability $p \in (0, 1)$. Following Kosorok [9], we require the densities at the quantiles to be positive for both treatment groups. We also suppose that there exists $\epsilon > 0$ such that $H_k(F_k^{-1}(p) + \epsilon) > 0$, $k = 1, 2$. This condition is needed to ensure sufficient follow-up in order to be able to estimate each quantile of interest.

We denote as $\hat{F}_k$, $k = 1, 2$, the Kaplan-Meier estimator of F_k, from which we derive $\hat{F}_k^{-1}(p)$, the estimator of the inverse distributions at p. Our method is based on the asymptotic distribution of $\hat{F}_k^{-1}(p)$ as derived in Kosorok [9]. In this work, the asymptotic variance depends on the density at the quantile $F_k^{-1}(p)$, which needs to be estimated in order to construct a statistical test. This estimator is denoted by $\hat{f}_k$ which we propose to estimate by either kernel density estimation or a resampling procedure inspired by Lin et al. [11] This method consists on generating multiple realizations of the centered Gaussian variable with variance σ^2, and then performing the least squares estimation which gives directly an estimation of the density at the quantile of interest $F_k^{-1}(p)$ for a given probability p and group k. We propose an automatic grid-search algorithm in order to choose the variance of the generated Gaussian. Our procedure has the advantage of providing an estimation of the density directly at the point of interest, contrary to kernel density estimation which requires an estimation at all data points. Indeed, it is well known [13] that kernel density estimators have a slow rate of convergence (in particular, slower than $n^{-1/2}$), that depends on the regularity of the density. For instance, if the density is assumed to be differentiable, then the rate of convergence is of order $n^{-1/3}$ for an optimal bandwidth of order $n^{-1/3}$. On the other hand, the resampling procedure estimates the density at a single point, thus achieving the $n^{-1/2}$ parametric rate of convergence. Further details on the resampling and kernel density methods are provided in Supplemental material.

2.1 Univariate test

We are interested in testing the null hypothesis $\mathcal{H}_0 : F_1^{-1}(p) = F_2^{-1}(p)$ against the alternative hypothesis $\mathcal{H}_1 : F_1^{-1}(p) - F_2^{-1}(p) = \Delta$, for a difference in quantiles $\Delta \in \mathbb{R}, \Delta \neq 0$. Such a null hypothesis allows to investigate the benefit, if any, of the experimental arm over the control arm at a given quantile. Assuming the conditions outlined in Section 2 hold for groups $k = 1, 2$, it follows from Lemma 1 from Kosorok[9], with theoretical derivations detailed in Supplemental material,

$$\sqrt{n}(\hat{F}_k^{-1}(p) - F_k^{-1}(p)) \xrightarrow{d} \mathcal{N}\left(0, (1-p)^2 \frac{\phi_k}{\mu_k f_k(F_k^{-1}(p))^2}\right) \text{ as } n \to \infty,$$

where

$$\phi_k = \int_0^{F_k^{-1}(p)} \frac{d\Lambda_k(x)}{H_k(x)}.$$

We prove in Supplemental material that under $\mathcal{H}_0$,

$$\sqrt{n}(\hat{F}_1^{-1}(p) - \hat{F}_2^{-1}(p)) \xrightarrow{d} \mathcal{N}\left(0, \sigma^2_{\mathcal{H}_0}\right) \text{ as } n \to \infty,$$

where

$$\sigma^2_{\mathcal{H}_0} = (1-p)^2 \left(\frac{\phi_1}{\mu_1 f_1(F_1^{-1}(p))^2} + \frac{\phi_2}{\mu_2 f_2(F_2^{-1}(p))^2}\right).$$

We propose the following test statistic for the univariate test of equality of quantiles:

$$\mathcal{T}_n = \sqrt{n}\frac{\hat{F}_1^{-1}(p) - \hat{F}_2^{-1}(p)}{\hat{\sigma}_{\mathcal{H}_0}}, \text{ with}$$
$$\hat{\sigma}^2_{\mathcal{H}_0} = (1-p)^2 \left(\frac{\hat{\phi}_1}{\hat{\mu}_1 \hat{f}_1(\hat{F}_1^{-1}(p))^2} + \frac{\hat{\phi}_2}{\hat{\mu}_2 \hat{f}_2(\hat{F}_2^{-1}(p))^2}\right),$$

where $\hat{\phi}_1$ and $\hat{\phi}_2$ are obtained by the usual Greenwood's estimate of the Kaplan-Meier variance, and $\hat{f}_1(\hat{F}_1^{-1}(p))$, $\hat{f}_2(\hat{F}_2^{-1}(p))$ are consistent estimators for the densities, such as kernel density estimators or the resampling procedure inspired by Lin et al.[11]

Then the following results hold:

1. Under $\mathcal{H}_0 : F_1^{-1}(p) = F_2^{-1}(p)$, $\mathcal{T}_n \xrightarrow{d} \mathcal{N}(0,1)$ as $n \to \infty$.
2. Under $\mathcal{H}_1 : F_1^{-1}(p) - F_2^{-1}(p) = \Delta$, $\mathcal{T}_n - \sqrt{n}\frac{\Delta}{\hat{\sigma}_{\mathcal{H}_0}} \xrightarrow{d} \mathcal{N}(0,1)$ as $n \to \infty$.

For a test with type I error α and power $1-\beta$, as n goes to infinity,

$$P_{\mathcal{H}_0}(|\mathcal{T}_n| > q_{1-\frac{\alpha}{2}}) \to \alpha,$$

where $q_{1-\frac{\alpha}{2}}$ is the quantile of order $1 - \alpha/2$ of the standard normal distribution.

Let Φ be the cumulative distribution function of the standard normal distribution. From the asymptotic distribution of $\mathcal{T}_n$ under $\mathcal{H}_1$, we derive the following asymptotic formula for the power of the test:

$$1-\beta \approx 1-\Phi\left(q_{1-\frac{\alpha}{2}}-\frac{\sqrt{n}}{\hat{\sigma}_{\mathcal{H}_0}}\Delta\right)+\Phi\left(-q_{1-\frac{\alpha}{2}}-\frac{\sqrt{n}}{\hat{\sigma}_{\mathcal{H}_0}}\Delta\right).$$

Details and proofs can be found in Supplemental material.

2.2 Multivariate test

We now present general results for multivariate two-sample tests of equality of quantiles. The proofs are provided in Supplemental material. We aim to test, for a given J, the null hypothesis $\mathcal{H}_0 : F_1^{-1}(p_j) = F_2^{-1}(p_j)$, $j = 1, ..., J$ against the alternative hypothesis $\mathcal{H}_1 : F_1^{-1}(p_j) - F_2^{-1}(p_j) = \Delta_j, \exists j : \Delta_j \neq 0$.

Assuming the conditions outlined in section 2 are satisfied, then for $k = 1, 2$:

$$\sqrt{n}\begin{bmatrix}\dfrac{\hat{F}_k^{-1}(p_1)-F_k^{-1}(p_1)}{f_k(F_k^{-1}(p_1))}\\ \vdots \\ \dfrac{\hat{F}_k^{-1}(p_J)-F_k^{-1}(p_J)}{f_k(F_k^{-1}(p_J))}\end{bmatrix} \xrightarrow{d} \mathcal{N}(0,\Upsilon_{F_k}) \text{ as } n\to\infty,$$

where:

$$(\Upsilon_{F_k})_{jl} = \begin{cases}\dfrac{(1-p_j)^2\int_0^{F_k^{-1}(p_j)}\dfrac{d\Lambda_k(x)}{H_k(x)}}{\mu_k\left(f_k(F_k^{-1}(p_j))\right)^2}, \text{if } j=l\\ \dfrac{(1-p_j)(1-p_l)\int_0^{F_k^{-1}(p_j)\wedge F_k^{-1}(p_l)}\dfrac{d\Lambda_k(x)}{H_k(x)}}{\mu_k f_k(F_k^{-1}(p_j))f_k(F_k^{-1}(p_l))}, \text{otherwise.}\end{cases}$$

It follows that, under $\mathcal{H}_0$,

$$\mathcal{Z}_n = \sqrt{n}\begin{bmatrix}\hat{F}_1^{-1}(p_1)-\hat{F}_2^{-1}(p_1)\\ \vdots \\ \hat{F}_1^{-1}(p_J)-\hat{F}_2^{-1}(p_J)\end{bmatrix} \xrightarrow{d} \mathcal{N}(0,\Psi) \text{ as } n\to\infty,$$

where $\Psi = \Upsilon_{F_1} + \Upsilon_{F_2}$. In order to implement the test, we assume Ψ to be invertible. For the multivariate test of equality of quantiles, our test statistic has the following form:

$$\mathfrak{T}_n = \mathcal{Z}_n^T \hat{\Psi}^{-1} \mathcal{Z}_n,$$

where $\hat{\Psi}$ is obtained by replacing each component by its estimate, as in the univariate case.

Then the following results hold:

1. Under $\mathcal{H}_0 : F_1^{-1}(p_j) = F_2^{-1}(p_j), j = 1, ..., J$, $\mathfrak{T}_n \xrightarrow{d} \chi^2_J$ as $n \to \infty$.
2. Under $\mathcal{H}_1 : F_1^{-1}(p_j) - F_2^{-1}(p_j) = \Delta_j, j = 1, ..., J$, $\mathfrak{T}_n$ is asymptotically equivalent to $\chi^2_J(\Psi^{-1/2}\xi)$, an uncentered chi-squared distribution with J degrees of freedom and mean $\Psi^{-1/2}\xi$, with

$$\xi = \sqrt{n} \begin{bmatrix} \Delta_1 \\ \vdots \\ \Delta_J \end{bmatrix}.$$

The power of the multivariate test for equality of quantiles at level α as $n \to \infty$ expresses as:

$$1 - \beta \approx 1 - F_{\chi^2_J(\Psi^{-1/2}\xi)}(q_{J,1-\alpha}),$$

where $F_{\chi^2_J(\Psi^{-1/2}\xi)}$ is the cumulative distribution function of the uncentered chi-squared distribution with J degrees of freedom and mean $\Psi^{-1/2}\xi$, and $q_{J,1-\alpha}$ denotes the quantile of order $1 - \alpha$ of the chi-squared distribution with J degrees of freedom.

3 Illustration and results

The proposed method for univariate and multivariate tests for quantiles comparison is relevant in two main application frameworks. First, it is useful in sample size planning scenarios where one is interested in designing a clinical trial to compare treatment effects in the quantile scale. In this case, our method enables the calculation of statistical power for a given sample size at a fixed significance level. Similarly, it can be used to determine the minimum sample size required to achieve sufficient power for a test at a fixed level. Second, the method can be applied when survival data from both control and experimental arms are available, and we are interested in testing the hypothesis of equality of quantiles between two survival distributions. Both applications are presented in this section.

3.1 Planning a clinical trial

The results derived in the previous section allow sample size and power calculations for tests of equality of quantiles in the context of planning clinical trials in the presence of censoring. Assuming known distributions for survival times and censoring, one can compute the explicit power obtained by the test, or in an equivalent way, derive the minimum sample size required in order to achieve a fixed power.

We present simulations to illustrate the planning of a clinical trial using the proposed test of equality of quantiles. Two versatile scenarios were considered in the subsequent results, inspired by Eaton et al.[14], which allow to illustrate multiple realistic frameworks including proportional and nonproportional survival (Figure 1). Groups $k = 1, 2$ correspond to the control and experimental arm, respectively. In all scenarios, survival time in the control arm follows an exponential distribution with rate λ_a.

The survival time distribution in the experimental arm is specified as follows, for each simulation scenario:

- Scenario 1 (proportional hazards): Exponential with rate λ_b.
- Scenario 2 (late differences): Piecewise exponential with rate λ_a until time t_{cut} and λ_b onward.

In all scenarios, the distribution of censoring time is exponential with rate λ_{cens}. Using the expression derived in the previous section, it is possible to compute the analytical power as a function of the parameters for each scenario.

Indeed, for a fixed difference in quantiles equal to Δ, if both arms are exponential (scenario 1), one may deduce the expression for the rate of experimental arm as $\lambda_b = -\log(1-p)/(F_1^{-1}(p) - \Delta)$. Moreover, under independent censoring, it is possible to write the analytical expressions for the variance $\sigma^2_{\mathcal{H}_0}$:

$$\begin{aligned}
\phi_1 &= \frac{\lambda_a}{\lambda_a + \lambda_{\text{cens}}}(e^{(\lambda_a+\lambda_{\text{cens}})F_1^{-1}(p)} - 1) \\
\phi_2 &= \frac{\lambda_b}{\lambda_b + \lambda_{\text{cens}}}(e^{(\lambda_b+\lambda_{\text{cens}})F_2^{-1}(p)} - 1) \\
\sigma^2_{\mathcal{H}_0} &= \frac{(1-p)^2 \frac{\lambda_a}{\lambda_a+\lambda_{\text{cens}}}(e^{(\lambda_a+\lambda_{\text{cens}})F_1^{-1}(p)} - 1)}{\hat{\mu}_1(\lambda_a e^{-\lambda_a F_1^{-1}(p)})^2} + \frac{(1-p)^2 \frac{\lambda_b}{\lambda_b+\lambda_{\text{cens}}}(e^{(\lambda_b+\lambda_{\text{cens}})F_2^{-1}(p)} - 1)}{\hat{\mu}_2(\lambda_b e^{-\lambda_b F_2^{-1}(p)})^2}.
\end{aligned}$$

These quantities allow us to have an explicit expression for the power of the test.

We derive similar results for the second scenario, where we observe nonproportional hazards and late treatment effects. We have the following expression for the quantile in the experimental arm:

$$F_2^{-1}(p) = \begin{cases} -\frac{\log(1-p)}{\lambda_a}, 0 \leq p < 1 - e^{-\lambda_a t_{\text{cut}}} \\ t_{\text{cut}} - \left(\frac{\log(1-p)+\lambda_a t_{\text{cut}}}{\lambda_b}\right), p \geq 1 - e^{-\lambda_a t_{\text{cut}}} \end{cases}$$

In order to ensure the realization of this scenario, we require that $F_1^{-1}(p) - t_{\text{cut}} > \Delta$, which is equivalent to $F_2^{-1}(p) > t_{\text{cut}}$ when specifying the parameters. For this scenario, we have the same ϕ_1 as the one where both arms are exponential, while the expression for ϕ_2 is now written as:

$$\phi_2 = \frac{\lambda_a}{\lambda_a + \lambda_{\text{cens}}}(e^{(\lambda_a+\lambda_{\text{cens}})t_{\text{cut}}} - 1) + \left(\frac{\lambda_b}{\lambda_b + \lambda_{\text{cens}}} e^{(\lambda_a-\lambda_b)t_{\text{cut}}}\right)\left(e^{(\lambda_b+\lambda_{\text{cens}})F_2^{-1}(p)} - e^{(\lambda_b+\lambda_{\text{cens}})t_{\text{cut}}}\right)$$

In all simulations we compare the medians in both groups and we assume that the number of patients in each arm is the same. We choose λ_{cens} in order to have approximately 25% of censoring in each group. We fix the rate of the control group in both scenarios as $\lambda_a = 1.5$ and $t_{\text{cut}} = 0.2$ in scenario 2.

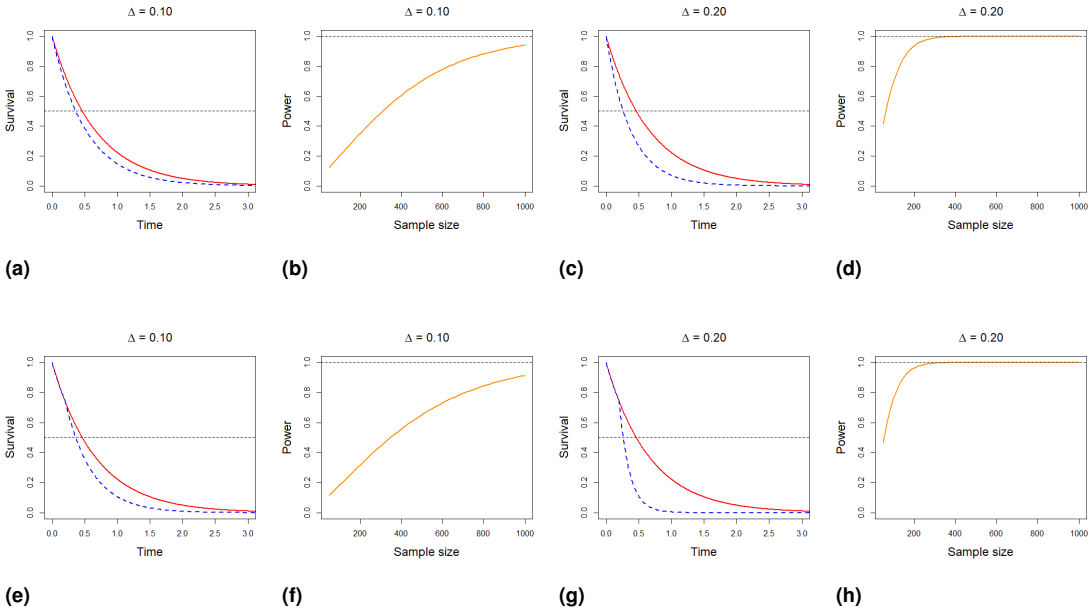

Figure 1. Comparison of scenarios. Top row: Scenario 1 with true survival curves and power analyses. Bottom row: Scenario 2 with similar comparisons. The solid line represents the control arm and the dashed line represents the experimental arm.

For these two scenarios, we assess the performance of the power formula on finite samples. For this, ten thousand simulations were performed to compare the asymptotic power obtained by the explicit formula to the empirical power obtained from simulations. Results shown in Table 1 confirm that the analytical formula provides a good approximation even with modest sample sizes and that type I error is well controlled.

Δ	Scenario 1		Scenario 2	
	Empirical	**Formula**	**Empirical**	**Formula**
0	0.047	0.05	0.047	0.05
0.1	0.714	0.703	0.782	0.766
0.2	1.000	1.000	1.000	1.000

Table 1. Type I error and Power of the test of equality of quantiles for sample size $n_i = 500$.

One interest of the explicit power formula is its ability to compute the minimum sample size required in order to detect a fixed difference at a desired power. We illustrate this application by fixing a desired power and treatment effect and comparing the minimum sample size required for each scenario when testing for the equality of medians. The results are provided in Table 2. Analytical power can be plotted at increasing quantile difference for various sample sizes, which is presented in Figure 2. Across both

Power	Δ	Scenario 1	Scenario 2
		Sample Size	Sample Size
0.95	0.1	1047	901
	0.2	214	173
0.90	0.1	846	729
	0.2	173	140
0.80	0.1	632	545
	0.2	129	105

Table 2. Minimal sample size per group.

scenarios, power increases with sample size, as expected. Differences between treatment arms at the median are illustrated in scenario 2 for $\Delta \in [0, 0.25]$ in order to satisfy the condition $F_1^{-1}(p) - t_{\text{cut}} > \Delta$.

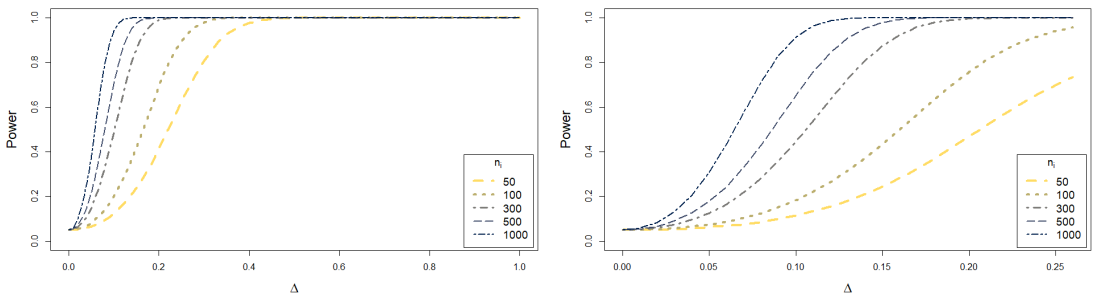

Figure 2. Power for various differences in quantiles in scenarios 1 (on the left) and 2 (on the right).

3.2 Application of the test on data from the OAK study

In this section, we apply our method to the OAK randomized clinical trial, registered under *ClinicalTrials.gov (NCT02008227)*. This study compared immunotherapy with chemotherapy in 850 patients with metastatic non-small-cell lung cancer, the primary endpoint being the overall survival. Following Mboup et al.[1], we use reconstructed survival data generated by the algorithm developed in Rittmeyer et al.[12] to emulate survival times for both treatment arms, enabling our analysis. The reconstructed Kaplan-Meier curves are seen in Figure 3.

The implementation of the test statistic requires the value of the density at the quantiles for both treatment arms. We compare two approaches for density estimation, kernel density estimation and an original resampling procedure inspired by Lin et al.[11], here referred to as KDE and LS respectively. In our implementation, the bandwidth parameter for the KDE is obtained through leave-one-out cross-validation. The LS method requires the specification of a variance for the generated Gaussians in the resampling procedure, which we propose to obtain using an automatic grid-search algorithm. Further

details on the LS method, variance selection and the KDE method can be found in Supplemental material.

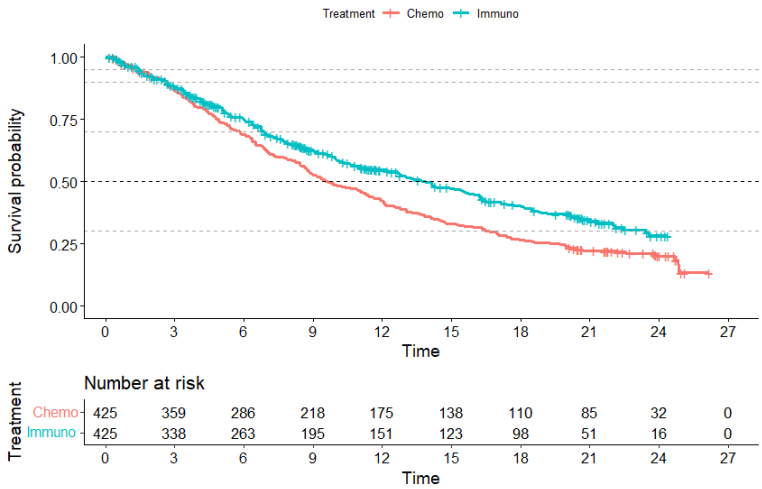

Figure 3. Reconstructed Kaplan-Meier curves. The dashed lines represent the survival quantiles at probabilities 0.05, 0.1, 0.3, 0.5 and 0.7.

3.2.1 Application of the univariate test We compute the power of the univariate test of equality of quantiles for OAK data. The test was applied at quantiles of order 0.3, 0.5 and 0.7, and differences between treatment arms are estimated for each quantile. The results are presented in Table 3.

For all quantiles considered, patients treated with immunotherapy have a positive survival average benefit compared with patients treated with immunotherapy, which can be directly interpreted in terms of survival time. Taking the median, for instance, we may say that, on average, patients from the immunotherapy group have 50% of chance to survive 4.04 months more than patients in the chemotherapy group.

At the median, we compare our approach with the test of equality of medians proposed in Tang and Jeong[6], which gives a p-value of 2.22×10^{-3} for this setting.

p	$\hat{\Delta}$	P-Value		Test Statistic	
		LS	KDE	LS	KDE
0.3	-1.01	1.13×10^{-2}	8.49×10^{-2}	-2.53	-1.72
0.5	-4.04	5.03×10^{-4}	5.35×10^{-3}	-3.48	-2.79
0.7	-6.76	4.39×10^{-9}	5.05×10^{-7}	-5.87	-5.02

Table 3. P-Values and Test Statistics for LS and KDE Methods for the univariate test.

All methods lead to the same statistical conclusion of rejection of the null hypothesis at each of the tested quantiles. In all cases, the test with the LS method for density estimation yields the most significant p-values.

3.2.2 Application of the multivariate test One advantage of the proposed test of equality of quantiles is its direct application for multivariate two-sample tests of equality of quantiles. In this section we present the results obtained for the comparison of pairs of quantiles, which can be generalized in order to compare any set of J quantiles. We apply the multivariate test to three pairs of quantiles: $\{(0.05, 0.1), (0.1, 0.5), (0.5,0.7)\}$. The results are provided in Table 4, where either KDE or LS were used for computing the density at the quantiles which are needed for the estimation of the matrix of variance-covariance of the test statistic.

p	$\hat{\Delta}$	P-Value		Test Statistic	
		LS	KDE	LS	KDE
0.05, 0.1	-0.03, -0.06	9.83×10^{-1}	9.91×10^{-1}	0.03	0.02
0.1, 0.5	-0.06, -4.04	3.39×10^{-2}	1.18×10^{-1}	6.77	4.28
0.5, 0.7	-4.04, -6.76	4.61×10^{-6}	1.80×10^{-3}	24.58	12.65

Table 4. P-Values and Test Statistics for LS and KDE Methods for the multivariate test.

The first row of Table 4 corresponds to the scenario where the null hypothesis is satisfied. In this case, the null hypothesis is not rejected by both methods with p-values close to 1. In the second row, we have a case where the difference of quantiles is close to zero (equal to 0.06 in absolute value) for one of the probabilities and close to 4 in absolute value for the other. For a test of level 0.05, one rejects the null hypothesis when using the LS method for density estimation and does not reject it when the density is estimated by the KDE procedure. This is the only case among the three scenarios where, depending on the density estimation procedure, the conclusion of the test changes. This suggests a loss of power for the KDE procedure, which might be explained by the increased variability in this method due to its need to estimate the density at all points.

Lastly, we explore a scenario where there is a marked difference in quantiles for both probabilities, equal in absolute value to 4.04 and 6.76 for the survival quantiles 0.5 and 0.7 respectively. In this case, both methods reject the null hypothesis, and the procedure that uses LS density estimation is the most significant one.

4 Discussion

In this paper we derived the analytical expressions for the power calculation for the univariate and multivariate tests of equality of quantiles proposed by Kosorok[9]. The explicit formulas can be used in different situations when evaluating the effects of a new treatment against standard of care, such as computing minimum sample size when planning clinical trials or comparing quantiles in the presence of clinical data. The power formula was analytically derived and its asymptotic behavior was studied in simulations for the scenarios where there are proportional and nonproportional hazards. The power formula can be derived for general situations, by assuming different distributions for survival and censoring. The proposed test was illustrated in the context of immuno-oncology trials with late treatment

effects and nonproportional hazards. Estimation techniques are needed in order to perform the necessary power calculations for the test in presence of data. We showed the results obtained by using kernel density estimation as well as a resampling technique proposed by us, with an improved power for the resampling approach.

One major advantage of our proposed method is that it allows for multivariate tests, which can be further extended to group sequential clinical trials with staggered entry of patients and several interim analyzes. Furthermore, although the proposed test is designed for detecting the differences in quantiles of survival times, one could extend this approach to investigate co-primary endpoints to assess the effect of a randomized treatment jointly on the hazard and a given quantile or on the Restricted Mean Survival Time (RMST) [14] and a given quantile. Indeed, there is a subtle connection between RMST and percentile of survival because in practice, the choice of a clinically relevant restriction time imposes a percentile of survival. This is left to future research work.

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Declaration of conflicting interests

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Code availability

All data processing and statistical analysis were performed with the R statistical computing software version 4.3.2. The code used to perform all the simulations and the real data analysis is available at https://github.com/beafarah/dens-estimation-at-quantile/.

Supplemental material

Supplemental material for this article is available online.

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Supplementary materials: Univariate and multivariate tests of equality of quantiles with right-censored data

Contents

1 Proofs and Technical details

1.1 Univariate test

In this section, we present the proofs for the results in Section 2.1 of the main document, for the univariate test. We first recall the expression of the statistical test in the univariate case.

$$\mathcal{T}_n = \sqrt{n}\frac{\hat{F}_1^{-1}(p) - \hat{F}_2^{-1}(p)}{\hat{\sigma}_{\mathcal{H}_0}}, \text{ with}$$
$$\hat{\sigma}^2_{\mathcal{H}_0} = (1-p)^2\left(\frac{\hat{\phi}_1}{\hat{\mu}_1\hat{f}_1(\hat{F}_1^{-1}(p))^2} + \frac{\hat{\phi}_2}{\hat{\mu}_2\hat{f}_2(\hat{F}_2^{-1}(p))^2}\right).$$

Result 1. *Under* $\mathcal{H}_0 : F_1^{-1}(p) = F_2^{-1}(p)$, $\mathcal{T}_n \xrightarrow{d} \mathcal{N}(0,1)$ *as* $n \to \infty$

Proof. From Lemma 1 from Kosorok[1], for $k = 1, 2$,

$$\hat{F}_k^{-1}(p) - F_k^{-1}(p) = \frac{\hat{F}_k(F_k^{-1}(p)) - p}{f_k(F_k^{-1}(p))} + o_p\left(\frac{1}{\sqrt{n_k}}\right)$$

It follows from Theorem 6.3.1 from Fleming and Harrington[2] that:

$$\sqrt{n_k}\left(\frac{\hat{F}_k(F_k^{-1}(p)) - p}{f_k(F_k^{-1}(p))}\right) \xrightarrow{d} \mathcal{N}\left(0, (1-p)^2\frac{\phi_k}{f_k(F_k^{-1}(p))}\right), \text{ with}$$

$$\phi_k = \int_0^{F_k^{-1}(p)} \frac{d\Lambda_k(x)}{H_k(x)}.$$

Under $\mathcal{H}_0$, from the independence between treatment groups, as $n \to \infty$, we have that

$$\sqrt{n}\left[\frac{\hat{F}_1(F_1^{-1}(p)) - p}{f_1(F_1^{-1}(p))} - \frac{\hat{F}_2(F_2^{-1}(p)) - p}{f_2(F_2^{-1}(p))}\right] \xrightarrow{d} \mathcal{N}\left(0,\ (1-p)^2\left[\frac{\phi_1}{\mu_1 f_1(F_1^{-1}(p))^2} + \frac{\phi_2}{\mu_2 f_2(F_2^{-1}(p))^2}\right]\right)$$

Then, $\hat{\sigma}_{\mathcal{H}_0} \to \sigma_{\mathcal{H}_0}$ as $n \to \infty$ from the consistency of Greenwood's estimator of the Kaplan-Meier variance, the consistency of the density estimators and the consistency of $\hat{\mu}_k$, $k = 1, 2$. Finally under $\mathcal{H}_0$, we have the decomposition

$$\hat{F}_1^{-1}(p) - \hat{F}_2^{-1}(p) = \hat{F}_1^{-1}(p) - F_1^{-1}(p) - (\hat{F}_2^{-1}(p) - F_2^{-1}(p)),$$

which concludes the proof.

Result 2. *Under* $\mathcal{H}_1 : F_1^{-1}(p) - F_2^{-1}(p) = \Delta$, $\mathcal{T}_n - \sqrt{n}\frac{\Delta}{\hat{\sigma}_{\mathcal{H}_0}} \xrightarrow{d} \mathcal{N}(0,1)$ *as* $n \to \infty$

Proof. Under $\mathcal{H}_1$,

$$\sqrt{n}(\hat{F}_1^{-1}(p) - \hat{F}_2^{-1}(p)) = \sqrt{n}(\hat{F}_1^{-1}(p) - F_1^{-1}(p)) - \sqrt{n}(\hat{F}_2^{-1}(p) - F_2^{-1}(p)) + \sqrt{n}\Delta.$$

We denote

$$Z_n = \sqrt{n}(\hat{F}_1^{-1}(p) - F_1^{-1}(p)) - \sqrt{n}(\hat{F}_2^{-1}(p) - F_2^{-1}(p)).$$

Then, from Lemma 1 from Kosorok[1],

$$Z_n = \sqrt{n}\left(\frac{\hat{F}_1(F_1^{-1}(p)) - p}{f_1(F_1^{-1}(p))}\right) - \sqrt{n}\left(\frac{\hat{F}_2(F_2^{-1}(p)) - p}{f_2(F_2^{-1}(p))}\right) + o_p\left(\frac{1}{\sqrt{n}}\right).$$

It follows, for $n \to \infty$:

$$Z_n \xrightarrow{d} \mathcal{N}\left(0, \frac{(1-p)^2\phi_1}{\mu_1 f_1(F_1^{-1}(p))^2} + \frac{(1-p)^2\phi_2}{\mu_2 f_2(F_2^{-1}(p))^2}\right)$$

From the consistency of $\hat{\sigma}_{\mathcal{H}_0}$, we therefore have $Z_n/\hat{\sigma}_{\mathcal{H}_0} \xrightarrow{d} \mathcal{N}(0,1)$, which gives the desired result using the relation

$$\mathcal{T}_n = Z_n/\hat{\sigma}_{\mathcal{H}_0} + \sqrt{n}\Delta/\hat{\sigma}_{\mathcal{H}_0}.$$

Result 3. *We have the following asymptotic formula for the power of the test of level α:*

$$1 - \beta \approx 1 - \Phi\left(q_{1-\alpha/2} - \frac{\sqrt{n}}{\hat{\sigma}_{\mathcal{H}_0}}\Delta\right) + \Phi\left(-q_{1-\alpha/2} - \frac{\sqrt{n}}{\hat{\sigma}_{\mathcal{H}_0}}\Delta\right)$$

where Φ is the cumulative distribution function of the standard normal variable and $q_{1-\alpha/2}$ is the quantile of level $1-\alpha/2$ of the standard normal distribution.

Proof. Using the derived expression for the test statistic and denoting as $q_{1-\frac{\alpha}{2}}$ the quantile of order $1-\frac{\alpha}{2}$ of the standard normal distribution,

$$\begin{aligned}
1 - \beta &= P_{\mathcal{H}_1}(|\mathcal{T}_n| > q_{1-\frac{\alpha}{2}}) \\
&= P_{\mathcal{H}_1}\left(\sqrt{n}\left|\frac{\hat{F}_1^{-1}(p) - \hat{F}_2^{-1}(p)}{\hat{\sigma}_{\mathcal{H}_0}}\right| > q_{1-\frac{\alpha}{2}}\right) \\
&= P_{\mathcal{H}_1}\left(\sqrt{n}\left|\left(\frac{\hat{F}_1^{-1}(p) - F_1^{-1}(p)}{\hat{\sigma}_{\mathcal{H}_0}}\right) - \left(\frac{\hat{F}_2^{-1}(p) - F_2^{-1}(p)}{\hat{\sigma}_{\mathcal{H}_0}}\right) + \frac{\Delta}{\hat{\sigma}_{\mathcal{H}_0}}\right| > q_{1-\alpha/2}\right) \\
&\approx P_{\mathcal{H}_1}\left(\frac{\sqrt{n}}{\hat{\sigma}_{\mathcal{H}_0}}\left(\frac{\hat{F}_1(F_1^{-1}(p)) - p}{f_1(F_1^{-1}(p))} - \frac{\hat{F}_2(F_2^{-1}(p)) - p}{f_2(F_2^{-1}(p))}\right) > q_{1-\alpha/2} - \frac{\sqrt{n}\Delta}{\hat{\sigma}_{\mathcal{H}_0}}\right) \\
&+ P_{\mathcal{H}_1}\left(\frac{\sqrt{n}}{\hat{\sigma}_{\mathcal{H}_0}}\left(\frac{\hat{F}_1(F_1^{-1}(p)) - p}{f_1(F_1^{-1}(p))} - \frac{\hat{F}_2(F_2^{-1}(p)) - p}{f_2(F_2^{-1}(p))}\right) < -q_{1-\alpha/2} - \frac{\sqrt{n}\Delta}{\hat{\sigma}_{\mathcal{H}_0}}\right) \\
&\approx P_{\mathcal{H}_1}\left(\frac{Z_n}{\hat{\sigma}_{\mathcal{H}_0}} > q_{1-\alpha/2} - \frac{\sqrt{n}\Delta}{\hat{\sigma}_{\mathcal{H}_0}}\right) + P_{\mathcal{H}_1}\left(\frac{Z_n}{\hat{\sigma}_{\mathcal{H}_0}} < -q_{1-\alpha/2} - \frac{\sqrt{n}\Delta}{\hat{\sigma}_{\mathcal{H}_0}}\right),
\end{aligned}$$

where the expression in the fourth equality comes from Lemma 1 from Kosorok[1]. We conclude from the convergence of $Z_n/\hat{\sigma}_{\mathcal{H}_0}$ towards a centered Gaussian random variable.

1.2 Multivariate test

In this section, we present the proofs for the results in Section 2.2 of the main document, for the multivariate test.

Result 4. *For $k = 1, 2$,*

$$\sqrt{n}\begin{bmatrix} \dfrac{\hat{F}_k^{-1}(p_1) - F_k^{-1}(p_1)}{f_k(F_k^{-1}(p_1))} \\ \vdots \\ \dfrac{\hat{F}_k^{-1}(p_J) - F_k^{-1}(p_J)}{f_k(F_k^{-1}(p_J))} \end{bmatrix} \xrightarrow{d} \mathcal{N}(0, \Upsilon_{F_k}) \text{ as } n \to \infty,$$

where:

$$(\Upsilon_{F_k})_{jl} = \begin{cases} \dfrac{(1-p_j)^2 \int_0^{F_k^{-1}(p_j)} \dfrac{d\Lambda_k(x)}{H_k(x)}}{\mu_k (f_k(F_k^{-1}(p_j)))^2}, \text{ if } j = l \\ \dfrac{(1-p_j)(1-p_k) \int_0^{F_k^{-1}(p_j) \wedge F_k^{-1}(p_l)} \dfrac{d\Lambda_k(x)}{H_k(x)}}{\mu_k f_k(F_k^{-1}(p_j)) f_k(F_k^{-1}(p_l))}, \text{ otherwise.} \end{cases}$$

Proof. From Lemma 1 in Kosorok[1], we have:

$$\begin{bmatrix} \hat{F}_k^{-1}(p_1) - F_k^{-1}(p_1) \\ \vdots \\ \hat{F}_k^{-1}(p_J) - F_k^{-1}(p_J) \end{bmatrix} = U_k + o_p(1/\sqrt{n_k}),$$

where

$$U_k = \begin{bmatrix} \dfrac{\hat{F}_k(F_k^{-1}(p_1)) - p_1}{f_k(F_k^{-1}(p_1))} \\ \vdots \\ \dfrac{\hat{F}_k(F_k^{-1}(p_J)) - p_J}{f_k(F_k^{-1}(p_J))} \end{bmatrix}.$$

From Theorem 6.3.1 from Fleming and Harrington[2], $\sqrt{n_k} U_k$ converges to a centered multivariate Gaussian random variable where its variance matrix has entries (j, l) equal to:

$$\frac{(1-p_j)(1-p_l) \int_0^{F_k^{-1}(p_j) \wedge F_k^{-1}(p_l)} \dfrac{d\Lambda_k(x)}{H_k(x)}}{f_k(F_k^{-1}(p_j)) f_k(F_k^{-1}(p_l))}.$$

The result follows since $n_k/n \to \mu_k$ as $n \to \infty$.

Result 5. *Under* $\mathcal{H}_0 : F_1^{-1}(p_j) = F_2^{-1}(p_j), j = 1, ..., J,$

$$\mathcal{Z}_n = \sqrt{n} \begin{bmatrix} \hat{F}_1^{-1}(p_1) - \hat{F}_2^{-1}(p_1) \\ \vdots \\ \hat{F}_1^{-1}(p_J) - \hat{F}_2^{-1}(p_J) \end{bmatrix} \xrightarrow{d} \mathcal{N}(0, \Psi) \text{ as } n \to \infty,$$

where $\Psi = \Upsilon_{F_1} + \Upsilon_{F_2}$.

The test statistic, expressed as $\mathfrak{T}_n = \mathcal{Z}_n^T \Psi^{-1} \mathcal{Z}_n$, *converges in distribution towards a* χ^2_J *as* $n \to \infty$ *under* $\mathcal{H}_0$.

Proof. Since the two treatment groups are independent, we have under $\mathcal{H}_0$

$$\sqrt{n} \begin{bmatrix} \hat{F}_1^{-1}(p_1) - \hat{F}_2^{-1}(p_1) \\ \vdots \\ \hat{F}_1^{-1}(p_J) - \hat{F}_2^{-1}(p_J) \end{bmatrix} = \sqrt{n} \begin{bmatrix} \dfrac{\hat{F}_1^{-1}(p_1) - F_1^{-1}(p_1)}{f_1(F_1^{-1}(p_1))} \\ \vdots \\ \dfrac{\hat{F}_1^{-1}(p_J) - F_1^{-1}(p_J)}{f_1(F_1^{-1}(p_J))} \end{bmatrix} - \sqrt{n} \begin{bmatrix} \dfrac{\hat{F}_2^{-1}(p_1) - F_2^{-1}(p_1)}{f_2(F_2^{-1}(p_1))} \\ \vdots \\ \dfrac{\hat{F}_2^{-1}(p_J) - F_2^{-1}(p_J)}{f_2(F_2^{-1}(p_J))} \end{bmatrix} + o_p(1/\sqrt{n}).$$

From Result 4,

$$\mathcal{Z}_n = \sqrt{n} \begin{bmatrix} \hat{F}_1^{-1}(p_1) - \hat{F}_2^{-1}(p_1) \\ \vdots \\ \hat{F}_1^{-1}(p_J) - \hat{F}_2^{-1}(p_J) \end{bmatrix} \xrightarrow{d} \mathcal{N}(0, \Psi),$$

where $\Psi = \Upsilon_{F_1} + \Upsilon_{F_2}$. From these results, we conclude that, under $\mathcal{H}_0$, $\mathfrak{T}_n \xrightarrow{d} \chi^2_J$ as $n \to \infty$.

Result 6. *Under* $\mathcal{H}_1 : F_1^{-1}(p_j) - F_2^{-1}(p_j) = \Delta_j, j = 1, ..., J,$ $\mathfrak{T}_n$ *is asymptotically equivalent to* $\chi^2_J(\Psi^{-1/2}\xi)$, *an uncentered chi-squared distribution with* J *degrees of freedom and mean* $\Psi^{-1/2}\xi$, *with*

$$\xi = \sqrt{n} \begin{bmatrix} \Delta_1 \\ \vdots \\ \Delta_J \end{bmatrix}.$$

We then have the following asymptotic formula for the power of the test of level α*:*

$$1 - \beta = F_{\chi^2_J(\Psi^{-1/2}\xi)}(q_{J,1-\alpha}),$$

denoting as $F_{\chi^2_J(\Psi^{-1/2}\xi)}$ *the cumulative distribution function of this chi-squared distribution and* $q_{J,1-\alpha}$ *as the quantile of order* $1 - \alpha$ *of the chi-squared distribution with* J *degrees of freedom.*

Proof. We denote:

$$Y_n = \sqrt{n}\begin{bmatrix} \hat{F}_1^{-1}(p_1) - F_1^{-1}(p_1) \\ \vdots \\ \hat{F}_1^{-1}(p_J) - F_1^{-1}(p_J) \end{bmatrix} - \sqrt{n}\begin{bmatrix} \hat{F}_2^{-1}(p_1) - F_2^{-1}(p_1) \\ \vdots \\ \hat{F}_2^{-1}(p_J) - F_2^{-1}(p_J) \end{bmatrix}.$$

Under $\mathcal{H}_1$, we write:

$$\mathcal{Z}_n = Y_n + \xi.$$

From Lemma 1 in Kosorok[1], we have:

$$Y_n = \sqrt{n}\begin{bmatrix} \frac{\hat{F}_1(F_1^{-1}(p_1)) - p_1}{f_1(F_1^{-1}(p_1))} \\ \vdots \\ \frac{\hat{F}_1(F_1^{-1}(p_J)) - p_J}{f_1(F_1^{-1}(p_J))} \end{bmatrix} - \sqrt{n}\begin{bmatrix} \frac{\hat{F}_2(F_2^{-1}(p_1)) - p_1}{f_2(F_2^{-1}(p_1))} \\ \vdots \\ \frac{\hat{F}_2(F_2^{-1}(p_J)) - p_J}{f_2(F_2^{-1}(p_J))} \end{bmatrix} + o_p(1/\sqrt{n}).$$

The first and second term on the right-hand side of this equation converge in distribution respectively to $\mathcal{N}(0, \Upsilon_{F_1})$ and $\mathcal{N}(0, \Upsilon_{F_2})$ as $n \to \infty$. Therefore,

$$Y_n \xrightarrow{d} \mathcal{N}(0, \Psi), \text{ as } n \to \infty,$$

and $\mathcal{Z}_n$ is asymptotically equivalent to a $\mathcal{N}(\xi, \Psi)$. From the consistency of $\hat{\Psi}$, $\mathcal{Z}_n^T \hat{\Psi}^{-1} \mathcal{Z}_n$ is asymptotically equivalent to $\chi^2_J(\Psi^{-1/2}\xi)$. We conclude from the definition of the power,

$$\begin{aligned} 1 - \beta &= P_{\mathcal{H}_1}(\mathfrak{T}_n > q_{J,1-\alpha}) \\ &\approx F_{\chi^2_J(\Psi^{-1/2}\xi)}(q_{J,1-\alpha}). \end{aligned}$$

2 Details on the estimation of the density

In the main document, two different methods are proposed for the estimation of $f_k(F_k^{-1}(p))$, $k = 1, 2$: a resampling procedure based on the method from Lin *et al.*[3] and a kernel density estimator. The first method only estimates the densities at one point, the quantile $F_k^{-1}(p)$, while the second method estimates the whole function $f_k(t)$ from which the estimator at the quantile is obtained by setting $t = F_k^{-1}(p)$. In Section 2.1 the resampling procedure is explained, while details for the kernel density estimator are provided in Section 2.2.

2.1 Resampling procedure

We propose a resampling procedure that allows to estimate $f(F^{-1}(p))$ the density at a given quantile, for a given probability $0 < p < 1$. We present a method inspired by Lin *et al.*[3] in order to perform such task in a resampling procedure. We require the densities at the quantiles to be strictly positive, and we

denote as $\hat{F}$ the consistent estimator for F obtained from the usual Kaplan-Meier estimation. Taking this estimator we obtain $\hat{F}^{-1}(p)$ the estimators of the inverse distribution at p. Then we propose the following resampling procedure:

1. Generate B realizations of the Gaussian $\varepsilon \sim \mathcal{N}(0, \sigma^2)$, denoted by $\varepsilon_1, ..., \varepsilon_B$
2. Calculate $\sqrt{n}\left(\hat{F}\left(\hat{F}^{-1}(p) + \frac{\varepsilon_b}{\sqrt{n}}\right) - p\right), b = 1, ..., B$ and denote them as y_b, then the least squares estimate of $f(F^{-1}(p))$ is $\hat{A} = (x'x)^{-1}x'Y$, where $x = (\varepsilon_1, ..., \varepsilon_B)^T$ and $Y = (y_1, ..., y_B)^T$

We advocate that the variance of the Gaussian variables must be carefully chosen as it may impact the quality of estimation of the density. To illustrate this phenomenon, we study the behavior of the Mean Squared Error (MSE) when the sample size and σ change. Based on those results, we propose a grid-search method to automatically choose an optimal value for σ.

In Figure 1, we illustrate the MSE for a range of values of σ when estimating the median of an exponential distribution with rate 1.5. The true value of the density at the median is 0.75 and censoring follows an exponential distribution with rate 0.12. We generate $B = 10000$ Gaussians and we replicate the code 100 times.

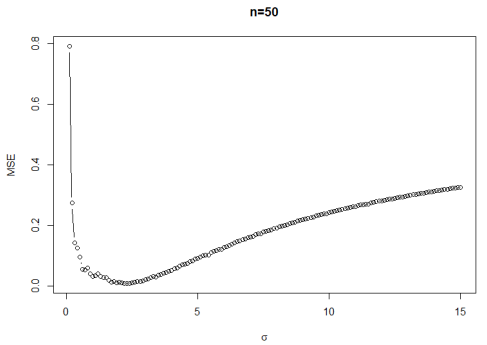
We notice that, for small sample sizes, the value of σ^2 plays an important role in the value of the MSE. Indeed, as one increases sample size, the region where MSE is minimized becomes broader, which allows for greater flexibility when choosing the variance within a wider interval of values where the MSE is small. Consequently, variance selection is particularly important when working with small sample sizes. For all sample sizes, we observe that the MSE decreases until it reaches a plateau, where it remains low over a range of σ values, before increasing again. Our goal is then to select a value of σ that lays in such interval, which grows broader as sample size increases.

To identify this plateau, we estimate the density at the quantile over a grid of σ values and examine the results in small neighborhoods. We look for an interval where the estimated density shows the smallest local variation within its region, and select σ a value within this interval.

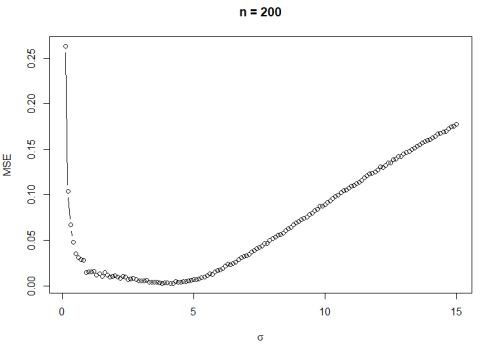
This procedure is illustrated for the estimation of the median of the exponential with rate 1.5, with exponential censoring with rate 0.12. We consider σ values ranging from 0 to 10 in increments of 0.05 and examine smaller neighborhoods, each containing 20 values for the estimated density at the median.

In Figure 2 we illustrate the estimation of the density at the median for each σ. The vertical line represents the selected σ by our procedure, which is equal to 3.65. We obtain an estimation of the density at the median equal to 0.72. In Figure 3, we illustrate the absolute difference between the estimated density at the median and the true value 0.75, for each σ. We see that our procedure selects a value of σ that lays inside the region where this difference is minimized.

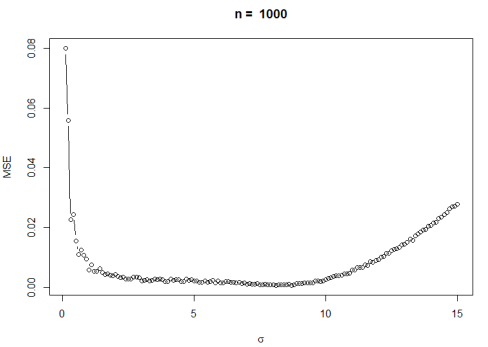
Our method has been illustrated in the exponential framework, but the same reasoning can be applied to other distributions. The procedure has been implemented in R and all code is available in order to perform the variance selection automatically using the proposed grid-search algorithm, as well as the density estimation at a given quantile using the selected variance.



(a) $n = 50$



(b) $n = 200$



(c) $n = 1000$

Figure 1. Comparison of MSE with respect to σ for different sample sizes.

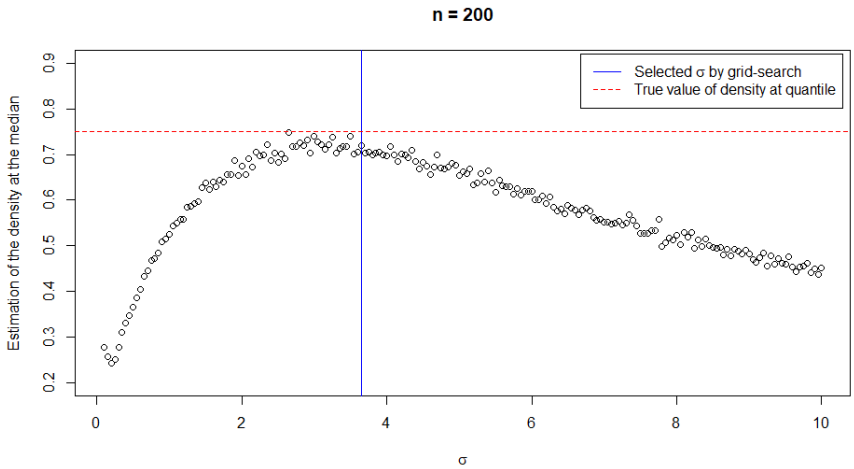


Figure 2. Example of density estimation at the median with respect to σ.

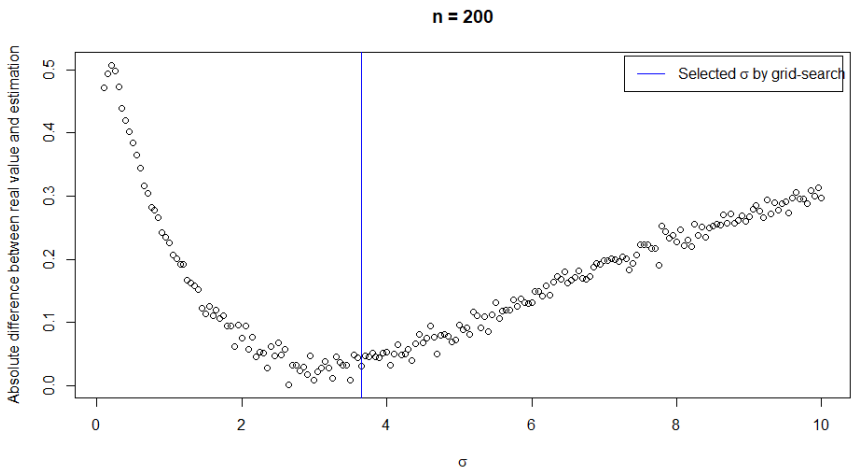


Figure 3. Absolute difference between the true density at median and its estimation by the proposed method, with respect to σ.

2.2 Kernel density estimation

In the presence of censoring, a typical kernel estimator of the density can be constructed by estimating the censoring distribution from the Kaplan-Meier estimator. In Földes *et al.*[4], Diehl and Stute[5] the following estimator has been proposed:

$$\hat{f}_h(t) = \frac{1}{nh} \sum_{i=1}^{n} \frac{\delta_i}{\hat{S}_{\text{cens}}(T_i)} K\left(\frac{T_i - t}{h}\right),$$

where $\hat{S}_{\text{cens}}$ is the Kaplan-Meier estimator of the censoring survival function and K a kernel satisfying standard conditions. In order to compute this estimator, the kernel and the bandwidth must be chosen. In our implementation, a Gaussian kernel was taken and the bandwidth was obtained from cross-validation. For the choice of the bandwidth, the goal of the method is to try to minimize the Integrated Squared Error (ISE), defined, for $k = 1, 2$, as:

$$\begin{aligned} \text{ISE}(\hat{f}_h) &= \int \left(\hat{f}_h(t) - f_k(t)\right)^2 dt \\ &= \int \hat{f}_h^2(t)dt - 2\int \hat{f}_h(t) f_k(t)dt + \int f_k^2(t)dt. \end{aligned}$$

In this expression the last term does not depend on h and can be omitted. On the other hand, the term $\int f_h(t) f_k(t)dt$ is estimated by:

$$\hat{J}(h) = \frac{1}{n(n-1)h} \sum_{i \neq j} K\left(\frac{T_i - T_j}{h}\right) \frac{\delta_{ik}\delta_{jk}}{\hat{S}_{\text{cens}}(T_i)\hat{S}_{\text{cens}}(T_j)}.$$

Using the consistency of the Kaplan-Meier estimator, it can easily be shown that this estimator converges in probability, as n tends to infinity, towards $\int \hat{f}_h(t) f_k(t)dt$ (see Marron and Padgett[6]). In conclusion, our cross-validated estimator is defined as the Gaussian kernel estimator with bandwidth chosen as the minimizer of $\int \hat{f}_h^2(t)dt - 2\hat{J}(h)$, that is:

$$\hat{h} = \arg\min_h \left\{ \int \hat{f}_h^2(t)dt - \frac{2}{n(n-1)h} \sum_{i \neq j} K\left(\frac{T_i - T_j}{h}\right) \frac{\delta_{ik}\delta_{jk}}{\hat{S}_{\text{cens}}(T_i)\hat{S}_{\text{cens}}(T_j)} \right\}.$$

We refer the reader to Marron and Padgett[6] for more details about the cross-validation bandwidth selector and theoretical results regarding its validity.

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