# Simultaneous Estimations of Multiple Contrasts of Quantiles

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**Abstract**

Statistical inference about the mean is common for distributions approximately following the normal law. Although the mean is popular, many researches in the health and social sciences involve skewed distributions and inferences about quantiles. Most existing multiple comparison procedures also require normality assumption. Very few methods exist for comparing the medians of independent samples or quantiles of several distributions in general. To our knowledge, there is no general-purpose method for constructing simultaneous confidence intervals for multiple contrasts of quantiles of arbitrary distributions. In this paper, we develop an asymptotic method for constructing such intervals. Small-sample performance of the proposed method is assessed in terms of simultaneous coverage probability and average width of the confidence intervals. Good coverage probabilities are observed even for extremely skewed distributions like the exponential. The proposed method is applied to biomedical data following a log-normal distribution and time-to-event data in survival analysis

*Keywords:* Asymptotic, Simultaneous inference, Density estimation, Multiple contrasts, Quantiles

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## 1. Introduction

Skewed data are very common in practice. For example household income and remission duration data from clinical trial for acute leukemia are positively skewed and they approximately follows log-normal or exponential distributions. For log-normal distributions, several methods have been proposed for constructing confidence intervals for single mean (Zhou & Gao, 1997; Olsson, 2005), for the ratio (or the difference) of two means (Krishnamoorthy & Mathew, 2003; Chen & Zhou, 2006) and multiple comparison of means (Schaarschmidt, 2012; Sadooghi-Alvandi & Malekzadeh, 2013). However, the arithmetic mean is sensitive to outlying observations and skewness. Other measures of location like median is preferred in this situation.

Many papers on using medians to compare distributions have focused on hypothesis testing. Examples are rank-based methods (Fung, 1980; Hettmansperger & McKean, 1998), the permutation test (Richter & McCann, 2013) and boostrap methods (Wilcox, 2006) for comparing medians of independent groups. Li et. al. (1996) proposed a control percentile test, chi-square test and bootstrap Kolmogorov-type test for comparing a single quantile, a finite set of quantiles, and the entire quantile functions of two distributions using a vertical quantile comparison function. Wilcox et. al. (2014) discussed a bootstrap method for comparing two independent groups using the lower and upper quantiles. Wu (2011) discusses seven methods for contructing confidence intervals for difference of median of time-to-event data. The problem of constructing simultaneous confidence intervals (SCIs) for several quantiles of a single distribution has been studied extensively; see for example Satten (1995), Liu et al. (2013) and Hayter (2014). Wilcox (1995) proposed a method for constructing SCIs for difference of several quantiles of two independent groups using bootstrap. However, a general method for constructing SCIs for multiple contrasts of quantiles is not available.

In this paper, we propose an asymptotic method for constructing SCIs for differences and ratios of quantiles. The method works for two or more independent samples from arbitrary distributions. Small sample properties of the proposed method are evaluated using samples from a variety of distributions such as exponential, cauchy, laplace, generalized extreme value, and mixture of normal. The coverage probabilities are observed to be close to the nominal level for most distributions of practical interest.

In Section 2.1, asymptotic SCIs for difference of quantiles is described and illustrations given for the case of three treatment groups. Section 2.2 describes asymptotic SCIs for ratios of quantiles. Section 2.3 includes development of the method for time-to-event data set. Section 3 describes the simulation study and shows the results. Seciton 3.1 includes the discussion of the results. Applications to real data sets are illustrated in Section 4. Concluding remarks are given in Section 5.

## 2. Multiple contrasts of quantiles

### *2.1. Difference of quantiles*

Let $\xi_{p,i}$ be the $p$th quantile of a probability function $f_i(\cdot)$ for group $i$, $\quad i = 1, 2, ..., k$, and let $\mathbf{C}$ be an $m \times k$ matrix containing $m$ contrasts. We are interested in constructing a $100(1-\alpha)\%$ simultaneous confidence intervals for the components of $\mathbf{C}\boldsymbol{\xi}_p$, where $\boldsymbol{\xi}_p = (\xi_{p,1}, \xi_{p,2}, ..., \xi_{p,k})^T$. For example, in multiple comparisons to a control, $m = k-1$, and $m = k(k-1)/2$ for all pairwise comparisons of quantiles. Consider independent samples of size $n_i$ from the probability density function $f_i(\cdot)$. It is well known that the $p$th sample quantile denoted by $\hat{\xi}_{p,i} \equiv x_{([n_i p])}$ follows a normal distribution asymptotically,

$$\sqrt{n_i}\left(\hat{\xi}_{p,i} - \xi_{p,i}\right) \xrightarrow{d} N\left(0, \frac{p(1-p)}{\left(f_i\left(\xi_{p,i}\right)\right)^2}\right), \quad 0 < p < 1, \quad i = 1, 2, ..., k,$$

where $f_i(\xi_{p,i})$ is the density value at the $p$th quantile. In other words,

$$\hat{\xi}_{p,i} \xrightarrow{d} N\left(\xi_{p,i}, \frac{p(1-p)}{n_i(f_i(\xi_{p,i}))^2}\right).$$

Let $\hat{\boldsymbol{\xi}}_p = (\hat{\xi}_{p,1}, \hat{\xi}_{p,2}, ..., \hat{\xi}_{p,k})^T$ be a vector of sample quantiles from $k$ independent samples. Then we have

$$\mathbf{C}\hat{\boldsymbol{\xi}}_p \xrightarrow{d} N_m(\mathbf{C}\boldsymbol{\xi}_p, \mathbf{C}\boldsymbol{\Sigma}\mathbf{C}^T),$$

where the covariance matrix $\mathbf{\Sigma}$ is a diagonal matrix with elements $\sigma_i^2 = p(1-p)/\left(n_i\left(f_i\left(\xi_{p,i}\right)\right)^2\right), \quad i = 1, 2, ..., k$. Note that the matrix $\mathbf{\Sigma}$ involves the density $f_i$ of the underlying probability distribution and that these densities are not necessarily from the same family. We use kernel density estimation (Rosenblatt, 1956; Parzen, 1962) to estimate $f$ and hence $\mathbf{\Sigma}$. The estimate of $\mathbf{\Sigma}$ is $\hat{\mathbf{\Sigma}}$ with diagonal elements ${\hat{\sigma_i}}^2 = p\left(1-p\right)/\left(n_i(\hat{f}_i(\hat{\xi}_{p,i}))^2\right)$, where $\hat{f}_i$ is the kernel density estimate of $f$ with a Gaussian kernel $K(\cdot)$,

$$\hat{f}_i(t) = \frac{1}{n_i h}\sum_{j=1}^{n_i} K\Big(\frac{t - x_{ij}}{h}\Big),$$

and $h$ is a bandwidth. We use Silverman's rule of thumb (Silverman, 1986) for the calculation of the bandwidth. The effect of using the true density at the true $p$th quantile, $f_i\left(\xi_{p,i}\right)$ as well as the kernel density estimate at the sample $p$th quantile, $\hat{f}_i(\hat{\xi}_{p,i})$, will be assessed using simulation later in Section 3.

Let $q_{1-\alpha}$ be the $\alpha$th equicoordinate quantile of a multivariate normal distribution with mean $\mathbf{0}$ and covariance $\mathbf{C}\hat{\mathbf{\Sigma}}\mathbf{C}^T$, calculated using the Genz and Bretz algorithm (Genz, 1992, 1993; Genz & Bretz, 2002). The correlation matrix $\hat{\boldsymbol{R}}$ associated with the covariance matrix, $\mathbf{C}\hat{\mathbf{\Sigma}}\mathbf{C}^T$ is given by $\mathbf{D}_{\hat{\sigma}}^{-1}\mathbf{C}\hat{\mathbf{\Sigma}}\mathbf{C}^T\mathbf{D}_{\hat{\sigma}}^{-1}$ where $\mathbf{D}_{\hat{\sigma}}^{-1}$ is the inverse of $\mathbf{D}_{\hat{\sigma}} = [\text{diag}(\mathbf{C}\hat{\mathbf{\Sigma}}\mathbf{C}^T)]^{1/2}$. Then the asymptotic $100(1-\alpha)\%$ SCIs for $\mathbf{c}_j\boldsymbol{\xi_p}, \quad j = 1, ..., m$, are given by

$$\mathbf{c}_j\hat{\boldsymbol{\xi}}_{\boldsymbol{p}} \pm q_{1-\alpha}\sqrt{\mathbf{c}_j^T\hat{\mathbf{\Sigma}}\mathbf{c}_j}, \quad j = 1, ..., m,$$

where $\mathbf{c}_j$ is a vector from the $j$th row of contrast matrix $\mathbf{C}$.

As an illustration, consider three independent samples, $k = 3$, where $p = 0.5$. The interest is to construct a $100(1-\alpha)\%$ SCIs for difference of medians, $\mathbf{C}\boldsymbol{\xi}_{0.5}$.

For multiple comparison to control, $m = 2$, contrast matrix $\mathbf{C} = \begin{pmatrix} 1 & 0 & -1 \\ 0 & 1 & -1 \end{pmatrix}$ and vector of estimated median, $\hat{\boldsymbol{\xi}}_{0.5} = (\hat{\xi}_{0.5,1}, \hat{\xi}_{0.5,2}, \hat{\xi}_{0.5,3})^T$, where $\hat{\xi}_{0.5,1}$, $\hat{\xi}_{0.5,2}$ and $\hat{\xi}_{0.5,3}$ are the median of the treatment 1, treatment 2 and the control group respectively. Then the joint distribution of $\boldsymbol{C}\hat{\boldsymbol{\xi}}_{0.5}$ is given by

$$\boldsymbol{C}\hat{\boldsymbol{\xi}}_{0.5} \xrightarrow{d} N_2\big(\boldsymbol{C}\boldsymbol{\xi}_{0.5}, \mathbf{C}\mathbf{\Sigma}\mathbf{C}^T\big),$$

where

$$\mathbf{C}\boldsymbol{\xi}_{0.5} = \begin{pmatrix} \xi_{0.5,1} - \xi_{0.5,3} \\ \xi_{0.5,2} - \xi_{0.5,3} \end{pmatrix}, \quad \mathbf{C}\mathbf{\Sigma}\mathbf{C}^T = \begin{pmatrix} {\sigma_1}^2 + {\sigma_3}^2 & {\sigma_3}^2 \\ {\sigma_3}^2 & {\sigma_2}^2 + {\sigma_3}^2 \end{pmatrix}$$

and

$${\sigma_i}^2 = \frac{1}{4n_i(f_i(\xi_i))^2}, \quad i = 1, 2, 3. \tag{1}$$

Then a $100(1-\alpha)\%$ SCIs for $\mathbf{c}_j\boldsymbol{\xi}_{0.5}, \quad j = 1, 2$ are given by

$$\mathbf{c}_j\hat{\boldsymbol{\xi}}_{0.5} \pm q_{1-\alpha}\sqrt{\mathbf{c}_j^T\hat{\mathbf{\Sigma}}\mathbf{c}_j}, \quad j = 1, 2.$$

For pairwise comparisons, $m = 3$. The contrast matrix $\mathbf{C} = \begin{pmatrix} 1 & -1 & 0 \\ 1 & 0 & -1 \\ 0 & 1 & -1 \end{pmatrix}$. The joint distribution of $\boldsymbol{C}\hat{\boldsymbol{\xi}}_{0.5}$ is given by

$$\boldsymbol{C}\hat{\boldsymbol{\xi}}_{0.5} \xrightarrow{d} N_3\big(\boldsymbol{C}\boldsymbol{\xi}_{0.5}, \mathbf{C}\mathbf{\Sigma}\mathbf{C}^T\big)$$

where

$$\mathbf{C}\boldsymbol{\xi}_{0.5} = \begin{pmatrix} \xi_{0.5,1} - \xi_{0.5,2} \\ \xi_{0.5,1} - \xi_{0.5,3} \\ \xi_{0.5,2} - \xi_{0.5,3} \end{pmatrix}, \quad \mathbf{C}\boldsymbol{\Sigma}\mathbf{C}^T = \begin{pmatrix} {\sigma_1}^2 + {\sigma_2}^2 & {\sigma_1}^2 & {\sigma_2}^2 \\ {\sigma_1}^2 & {\sigma_1}^2 + {\sigma_3}^2 & {\sigma_3}^2 \\ {\sigma_2}^2 & {\sigma_3}^2 & {\sigma_2}^2 + {\sigma_3}^2 \end{pmatrix}$$

Then a $100(1-\alpha)\%$ SCIs for $\mathbf{c}_j\boldsymbol{\xi}_{0.5}, \quad j = 1, 2, 3$ are given by

$$\mathbf{c}_j\hat{\boldsymbol{\xi}}_{0.5} \pm q_{1-\alpha}\sqrt{\mathbf{c}_j^T\hat{\boldsymbol{\Sigma}}\mathbf{c}_j}, \quad j = 1, 2, 3.$$

*2.2. Ratio of Quantiles*

Suppose that we have $k$ treatments. Given the vector of quantiles $\boldsymbol{\xi}_p = (\xi_{p,1}, \xi_{p,2}, ..., \xi_{p,k})^T$, we are interested in the vector of parameters $\boldsymbol{\rho} = (\rho_1, ..., \rho_r)$, where

$$\rho_l = \frac{\boldsymbol{a}_l^T\boldsymbol{\xi}_p}{\boldsymbol{b}_l^T\boldsymbol{\xi}_p} \quad l = 1, ..., r$$

and $r$ is the number of ratios. The vectors $\boldsymbol{a}_l = (a_{1l}, ..., a_{kl})$ and $\boldsymbol{b}_l = (b_{1l}, ..., b_{kl})$ have known elements with zeros everywhere and one at the position of treatment to be used. The interest is to construct SCIs for the ratio of quantiles, $\boldsymbol{\rho}$. One way of the derivation of confidence intervals for ratios is expressing the ratio problem in a linear form $L_l = (\rho_l\boldsymbol{b}_l - \boldsymbol{a}_l)^T\hat{\boldsymbol{\xi}}_p, \quad l = 1, ..., r$ (Fieller, 1954; Zerbe et al., 1982). $L_l$ approaches normal $N(0, \sigma^2_{L_l})$, where

$$\sigma^2_{L_l} = \mathrm{Var}(L_l) = (\rho_l\boldsymbol{b}_l - \boldsymbol{a}_l)^T\boldsymbol{\Sigma}(\rho_l\boldsymbol{b}_l - \boldsymbol{a}_l), \tag{2}$$

and $\mathrm{Var}(\hat{\boldsymbol{\xi}}_p) = \boldsymbol{\Sigma}$, a diagonal matrix with elements $\sigma_i^2, \quad i = 1, 2, ..., k$. The estimate ${\hat{\sigma_i}}^2$ is used when the true density is unknown. The associated correlation matrix $\mathbf{R}$ follows from standardizing (2). Note that the variance in (2) and $\mathbf{R}$ are functions of the unknown ratios $\rho_l$. Dilba et al. (2006) discuss the *plug-in* method for approximating $\mathbf{R}$. For $r = 1$, we have a single ratio. A $100(1-\alpha)\%$ SCI for $\rho$ using Fieller's theorem is the solution in $\rho$ of the inequality

$$\frac{L_l^2}{\mathrm{Var}(L_l)} \leqslant (q_{1-\alpha})^2 \tag{3}$$

The inequality in (3) can be expressed as a quadratic inequality in $\rho$

$$A\rho^2 + B\rho + C \leqslant 0 \tag{4}$$

where $A = (\boldsymbol{b}^T\hat{\boldsymbol{\xi}}_p)^2 - q^2\boldsymbol{b}^T\boldsymbol{\Sigma}\boldsymbol{b}$, $B = -2[(\boldsymbol{a}^T\hat{\boldsymbol{\xi}}_p)(\boldsymbol{b}^T\hat{\boldsymbol{\xi}}_p) - q^2\boldsymbol{a}^T\boldsymbol{\Sigma}\boldsymbol{b}]$, $C = (\boldsymbol{a}^T\hat{\boldsymbol{\xi}}_p)^2 - q^2\boldsymbol{a}^T\boldsymbol{\Sigma}\boldsymbol{a}$ and $q = q_{1-a}$ There are three possible solutions to the inequality in (4) depending the value of leading coefficient, $A$, and the discriminant, $B^2 - 4AC$. If $A > 0, B^2 - 4AC > 0$, the solution is a finite interval defined by two distinct roots. This is associated with situation when $\boldsymbol{b}_l^T\boldsymbol{\xi}_p$ is significantly different from 0. The other two cases result in either a region excluding the finite interval defined by the two distinct roots or the does not exclude any value at all on the $\rho$-axis. These conditions are discussed in Zerbe et al. (1982).

For more than one ratio, the SCIs are determined by solving inequalities of the type in (4) for each ratio separately.

*2.3. Time-to-event data*

We finally consider differences and ratios of survival times. In survival analysis, we are interest the distribution of survival times. The survival function $S(t)$ is defined as the probability that a subject survives longer than time $t$. Let $t(p)$ be the $p$th quantile of the distribution and $\hat{S}\big(t(p)\big)$ be the Kaplan Meier estimate (Kaplan & Meier, 1958) of the survival function at $t(p)$. Also, $\hat{t}(p)$ is the estimated $p$th quantile and its standard error is given by

$$\mathrm{se}\left(\hat{t}(p)\right) = \frac{1}{\hat{f}\left(\hat{t}(p)\right)}\mathrm{se}\left(\hat{S}\left(\hat{t}(p)\right)\right),$$

where $\hat{f}$ is an estimate of the probability density function. The standard error of $\hat{S}\left(\hat{t}(p)\right)$ is found by Greenwood's formula (Greenwood, 1926) while it is not easy to find $\hat{f}$. We use presmoothed kernel density estimation (Lopez-de-Ullibarri & Jacome, 2013) in survival analysis. For one survival function, an approximate $100(1-\alpha)\%$ confidence interval for $t(p)$ (Collett, 2015) is given by

$$\hat{t}(p) \pm z_{(1-\alpha/2)}\text{se}\left(\hat{t}(p)\right)$$

where $z_{(1-\alpha/2)}$ is the $\alpha$th quantile of the standard normal distribution.

*2.3.1. Difference of quantiles*

For multiple survival functions, let $\hat{\mathbf{t}}(p) = \left(\hat{t}_1(p), \hat{t}_2(p), ..., \hat{t}_k(p)\right)^T$ be a vector of the estimate $p$th quantiles. We propose an asymptotic simultaneous $100(1-\alpha)\%$ confidence interval for the $j$th contrast to be

$$\mathbf{c}_j\hat{\mathbf{t}}(p) \pm q_{1-\alpha}\sqrt{\mathbf{c}_j^T\hat{\mathbf{\Sigma}}\mathbf{c}_j}, \qquad j = 1, ..., m,$$

where $\hat{\mathbf{\Sigma}}$ is a diagonal covariance matrix whose elements are $\left(\text{se}\left(\hat{t}_i(p)\right)\right)^2 \quad i = 1, 2, ..., k$.

*2.3.2. Ratio of quantiles*

In clinical trials, ratios of median survival times for control and intervention groups are also of interest. These ratios have a convenient percent change interpretation. Assuming survival curves are approximately exponential, there is a simple method to obtain an approximate 95% confidence interval for the ratio $t_i(0.5)/t_j(0.5)$ (Friedman et al., 2010),

$$\left(\frac{\hat{t}_i(0.5)}{\hat{t}_j(0.5)}e^{-1.96S}, \frac{\hat{t}_i(0.5)}{\hat{t}_j(0.5)}e^{+1.96S}\right)$$

where $S = \sqrt{1/O_i + 1/O_i}$ and $O_i$ is the total number of events for group $i$. However, the exponential distribution is not commonly used for the distribution of survival times. If the assumption is relaxed, it is not simple to find the confidence interval because of the standard error. Confidence interval for the ratio of the $p$th quantiles of survival times can be computed by modifying the difference of quantiles. Let $\rho_{p,ij} = t_i(p)/t_j(p)$. Then $t_i(p) - \rho_{p,ij}t_j(p) = 0$. Thus the asymptotic simultaneous $100(1-\alpha)\%$ confidence interval for the $r$th contrast is

$$\mathbf{c}_r\hat{\mathbf{t}}(p) \pm q_{1-\alpha}\sqrt{\hat{\mathbf{c}}_r^T\hat{\mathbf{\Sigma}}\hat{\mathbf{c}}_r}, \quad r = 1, ..., m,$$

where the $i$th and $j$th components of $\mathbf{c}_r$ are 1 and $-\rho_{p,ij}$, respectively and $\hat{\rho}_{p,ij} = \hat{t}_i(p)/\hat{t}_j(p)$ in $\hat{\mathbf{c}}_r$. Therefore, the asymptotic simultaneous $100(1-\alpha)\%$ confidence interval for $\rho_{p,ij}$ is given by

$$\hat{\rho}_{p,ij} \pm \frac{q_{1-\alpha}}{\hat{t}_i(p)}\sqrt{(\text{se}(\hat{t}_i(p)))^2 + \hat{\rho}_{p,ij}^2(\text{se}(\hat{t}_i(p)))^2}.$$

From Fieller's theorem (Fieller, 1954), we have the $100(1-\alpha)\%$ confidence interval for $\rho_{p,ij}$,

$$\frac{1}{1-g}\left(\hat{\rho}_{p,ij} \pm \frac{q_{1-\alpha}}{\hat{t}_i(p)}\sqrt{(\text{se}(\hat{t}_i(p)))^2(1-g) + \hat{\rho}_{p,ij}^2(\text{se}(\hat{t}_i(p)))^2}\right)$$

where $g = q_{1-\alpha}^2(\text{se}(\hat{t}_j(p)))^2/(\hat{t}_j(p))^2$.

## 3. Simulation

In the simulation study, we focused on the asymptotic SCIs based on medians. Several distributions of theoretical interest are considered for this simulation. The distributions are normal, $\text{N}(\mu,\ \sigma)$, exponential, $\text{E}(\lambda)$, and mixture of two normal distributions, $0.5\text{N}(\mu_1,\ \sigma_1) + 0.5\text{N}(\mu_2,\ \sigma_2)$. We also consider Cauchy, $\text{C}(\mu, \sigma)$, Laplace, $\text{L}(\mu, \sigma)$ and generalized extreme value, $\text{G}(\mu, \sigma, \gamma)$, distributions, where $\mu$, $\sigma$, $\lambda$ and $\gamma$ are parameters for a location scale, rate and shape respectively. Some of the distributions are included for

theoretical interest. Three treatments, $k = 3$, are considered for each distribution. Then $m = 2$ for multiple comparisons to a control with treatment 1 as the control group or $m = 3$ for all pairwise comparisons. The sample sizes $n = 10, 30, 100, 500$ were used for each distribution. Two-sided nominal 95% SCIs are used for calculating coverage probability (CP) from 10000 replications. CP is defined as the probability that all true parameters are included in their respective SCIs. Average length (AL) of the SCIs corresponding to a CP is determined by calculated length of each of $m \times 10000$ SCIs and finding the average. Covariance matrix using the true density at the true median, $f(\xi)$, and the density estimate at the estimated median, $\hat{f}(\hat{\xi})$ are calculated for each of two situations: equicoordinate quantile based on the multivariate normal distribution ($MVNq$) and the multivariate $t$ distributions ($MVTq$) as shown in Tables 1, 2 and 3. Gaussian kernel density with Silverman's rule of thumb is used in estimating $\hat{f}$.

Table 1: Coverage probability (CP) and average length (AL) of 95% asymptotic SCIs for **multiple comparisons to a control** for **difference** of quantiles

| $n$ | $MVN_q$ | | | | $MVT_q$ | | | | Treatments | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | $\hat{f}(\hat{\xi})$ | | $f(\xi)$ | | $\hat{f}(\hat{\xi})$ | | $f(\xi)$ | | 1 | 2 | 3 |
| | CP | AL | CP | AL | CP | AL | CP | AL | | | |
| 10 | 0.943 | 2.6 | 0.965 | 2.5 | 0.957 | 2.7 | 0.974 | 2.6 | | | |
| 30 | 0.958 | 1.5 | 0.954 | 1.4 | 0.966 | 1.5 | 0.961 | 1.5 | N(0,1) | N(1,1) | N(2,1) |
| 100 | 0.962 | 0.8 | 0.952 | 0.8 | 0.961 | 0.8 | 0.950 | 0.8 | | | |
| 500 | 0.956 | 0.4 | 0.950 | 0.4 | 0.960 | 0.4 | 0.954 | 0.4 | | | |
| 10 | 0.922 | 1.2 | 0.943 | 1.2 | 0.937 | 1.3 | 0.954 | 1.2 | | | |
| 30 | 0.940 | 0.7 | 0.946 | 0.7 | 0.944 | 0.7 | 0.954 | 0.7 | E(1) | Exp(2) | Exp(3) |
| 100 | 0.943 | 0.4 | 0.950 | 0.4 | 0.942 | 0.4 | 0.948 | 0.4 | | | |
| 500 | 0.945 | 0.2 | 0.950 | 0.2 | 0.940 | 0.2 | 0.952 | 0.2 | | | |
| 10 | 0.983 | 4.4 | 0.907 | 3.1 | 0.987 | 4.6 | 0.922 | 3.3 | | | |
| 30 | 0.988 | 2.4 | 0.934 | 1.8 | 0.990 | 2.5 | 0.943 | 1.8 | C(0,1) | C(1,1) | C(2,1) |
| 100 | 0.983 | 1.2 | 0.943 | 1.0 | 0.985 | 1.2 | 0.948 | 1.0 | | | |
| 500 | 0.928 | 0.4 | 0.951 | 0.4 | 0.928 | 0.4 | 0.948 | 0.4 | | | |
| 10 | 0.968 | 2.9 | 0.881 | 2.0 | 0.977 | 3.0 | 0.900 | 2.1 | | | |
| 30 | 0.980 | 1.6 | 0.905 | 1.1 | 0.982 | 1.6 | 0.913 | 1.2 | L(0,1) | L(1,1) | L(2,1) |
| 100 | 0.986 | 0.8 | 0.922 | 0.6 | 0.987 | 0.8 | 0.926 | 0.6 | | | |
| 500 | 0.983 | 0.3 | 0.936 | 0.3 | 0.980 | 0.3 | 0.935 | 0.3 | | | |
| 10 | 0.954 | 3.0 | 0.963 | 2.9 | 0.962 | 3.2 | 0.970 | 3.0 | | | |
| 30 | 0.960 | 1.7 | 0.955 | 1.6 | 0.963 | 1.8 | 0.955 | 1.7 | G(0,1,0) | G(1,1,0) | G(2,1,0) |
| 100 | 0.957 | 0.9 | 0.952 | 0.9 | 0.961 | 1.0 | 0.953 | 0.9 | | | |
| 500 | 0.958 | 0.4 | 0.946 | 0.4 | 0.956 | 0.4 | 0.952 | 0.4 | | | |
| 10 | 0.943 | 2.9 | 0.964 | 2.8 | 0.955 | 3.1 | 0.976 | 3.0 | | | |
| 30 | 0.956 | 1.7 | 0.955 | 1.6 | 0.965 | 1.7 | 0.964 | 1.6 | 0.5N(0,1) | 0.5N(1,1) | 0.5N(2,1) |
| 100 | 0.963 | 0.9 | 0.950 | 0.9 | 0.961 | 0.9 | 0.950 | 0.9 | +0.5N(1,1) | +0.5N(2,1) | +0.5N(3,1) |
| 500 | 0.958 | 0.4 | 0.950 | 0.4 | 0.958 | 0.4 | 0.950 | 0.4 | | | |

Table 2: Coverage probability (CP) and average length (AL) of 95% aymptotic SCIs for **all pairwise comparisons** for **difference** of quantiles.

| $n$ | $MVN_q$ | | | | $MVT_q$ | | | | Treatments | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | $\hat{f}(\hat{\xi})$ | | $f(\xi)$ | | $\hat{f}(\hat{\xi})$ | | $f(\xi)$ | | 1 | 2 | 3 |
| | CP | AL | CP | AL | CP | AL | CP | AL | | | |
| 10 | 0.937 | 2.7 | 0.967 | 2.6 | 0.954 | 2.9 | 0.978 | 2.8 | | | |
| 30 | 0.956 | 1.6 | 0.958 | 1.5 | 0.961 | 1.6 | 0.962 | 1.5 | N(0,1) | N(1,1) | N(2,1) |
| 100 | 0.961 | 0.9 | 0.951 | 0.8 | 0.962 | 0.9 | 0.952 | 0.8 | | | |
| 500 | 0.956 | 0.4 | 0.949 | 0.4 | 0.958 | 0.4 | 0.951 | 0.4 | | | |
| 10 | 0.921 | 1.4 | 0.944 | 1.4 | 0.936 | 1.4 | 0.957 | 1.4 | | | |
| 30 | 0.941 | 0.8 | 0.944 | 0.8 | 0.941 | 0.8 | 0.952 | 0.8 | E(1) | E(2) | E(3) |
| 100 | 0.940 | 0.4 | 0.952 | 0.4 | 0.940 | 0.4 | 0.952 | 0.4 | | | |
| 500 | 0.941 | 0.2 | 0.947 | 0.2 | 0.938 | 0.2 | 0.954 | 0.2 | | | |
| 10 | 0.982 | 5.3 | 0.898 | 3.3 | 0.988 | 5.6 | 0.910 | 3.5 | | | |
| 30 | 0.990 | 2.6 | 0.928 | 1.9 | 0.993 | 2.6 | 0.939 | 1.9 | C(0,1) | C(1,1) | C(2,1) |
| 100 | 0.985 | 1.3 | 0.943 | 1.0 | 0.987 | 1.3 | 0.945 | 1.0 | | | |
| 500 | 0.919 | 0.5 | 0.946 | 0.5 | 0.926 | 0.5 | 0.947 | 0.5 | | | |
| 10 | 0.968 | 3.1 | 0.870 | 2.1 | 0.977 | 3.3 | 0.896 | 2.2 | | | |
| 30 | 0.986 | 1.7 | 0.902 | 1.2 | 0.985 | 1.7 | 0.913 | 1.2 | L(0,1) | L(1,1) | L(2,1) |
| 100 | 0.986 | 0.9 | 0.919 | 0.7 | 0.986 | 0.9 | 0.925 | 0.7 | | | |
| 500 | 0.983 | 0.4 | 0.933 | 0.3 | 0.984 | 0.4 | 0.937 | 0.3 | | | |
| 10 | 0.946 | 3.2 | 0.956 | 3.0 | 0.955 | 3.4 | 0.972 | 3.2 | | | |
| 30 | 0.956 | 1.8 | 0.954 | 1.7 | 0.962 | 1.9 | 0.956 | 1.8 | G(0,1,0) | G(1,1,0) | G(2,1,0) |
| 100 | 0.960 | 1.0 | 0.950 | 1.0 | 0.962 | 1.0 | 0.954 | 1.0 | | | |
| 500 | 0.960 | 0.4 | 0.948 | 0.4 | 0.958 | 0.4 | 0.950 | 0.4 | | | |
| 10 | 0.942 | 3.1 | 0.968 | 3.0 | 0.952 | 3.2 | 0.978 | 3.1 | | | |
| 30 | 0.958 | 1.8 | 0.957 | 1.7 | 0.959 | 1.8 | 0.962 | 1.7 | 0.5N(0,1) | 0.5N(1,1) | 0.5N(2,1) |
| 100 | 0.960 | 1.0 | 0.953 | 0.9 | 0.962 | 1.0 | 0.953 | 0.9 | +0.5N(1,1) | +0.5N(2,1) | +0.5N(3,1) |
| 500 | 0.955 | 0.4 | 0.948 | 0.4 | 0.958 | 0.4 | 0.953 | 0.4 | | | |

Table 3: Coverage probability (CP) and average length (AL) of 95% asymptotic SCIs for **multiple comparisons to a control** for **ratio** of quantiles.

| $n$ | $MVN_q$ | | | | $MVT_q$ | | | | Treatments | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | $\hat{f}(\hat{\xi})$ | | $f(\xi)$ | | $\hat{f}(\hat{\xi})$ | | $f(\xi)$ | | 1 | 2 | 3 |
| | CP | AL | CP | AL | CP | AL | CP | AL | | | |
| 10 | 0.935 | 1.1 | 0.976 | 1.0 | 0.949 | 1.2 | 0.985 | 1.1 | | | |
| 30 | 0.958 | 0.6 | 0.964 | 0.6 | 0.962 | 0.6 | 0.965 | 0.6 | N(0,1) | N(1,1) | N(2,1) |
| 100 | 0.958 | 0.3 | 0.956 | 0.3 | 0.961 | 0.3 | 0.950 | 0.3 | | | |
| 500 | 0.954 | 0.1 | 0.950 | 0.1 | 0.959 | 0.1 | 0.949 | 0.1 | | | |
| 10 | 0.873 | 8.2 | 0.935 | 10.0 | 0.885 | 8.9 | 0.944 | 10.5 | | | |
| 30 | 0.910 | 3.9 | 0.943 | 4.2 | 0.912 | 4.0 | 0.941 | 4.3 | E(1) | E(2) | E(3) |
| 100 | 0.933 | 2.0 | 0.950 | 2.1 | 0.932 | 2.0 | 0.949 | 2.1 | | | |
| 500 | 0.939 | 0.9 | 0.949 | 0.9 | 0.939 | 0.9 | 0.951 | 0.9 | | | |
| 10 | 0.981 | 3.3 | 0.930 | 1.9 | 0.984 | 3.4 | 0.942 | 1.9 | | | |
| 30 | 0.988 | 1.0 | 0.942 | 0.7 | 0.990 | 1.0 | 0.948 | 0.7 | C(0,1) | C(1,1) | C(2,1) |
| 100 | 0.983 | 0.5 | 0.945 | 0.4 | 0.983 | 0.5 | 0.952 | 0.4 | | | |
| 500 | 0.899 | 0.2 | 0.951 | 0.2 | 0.898 | 0.2 | 0.950 | 0.2 | | | |
| 10 | 0.964 | 1.6 | 0.898 | 0.8 | 0.971 | 1.8 | 0.913 | 0.9 | | | |
| 30 | 0.978 | 0.6 | 0.912 | 0.4 | 0.982 | 0.6 | 0.914 | 0.4 | L(0,1) | L(1,1) | L(2,1) |
| 100 | 0.985 | 0.3 | 0.922 | 0.2 | 0.984 | 0.3 | 0.922 | 0.2 | | | |
| 500 | 0.982 | 0.1 | 0.935 | 0.1 | 0.981 | 0.1 | 0.933 | 0.1 | | | |
| 10 | 0.934 | 1.1 | 0.978 | 1.0 | 0.944 | 1.2 | 0.984 | 1.1 | | | |
| 30 | 0.948 | 0.6 | 0.964 | 0.5 | 0.952 | 0.6 | 0.965 | 0.6 | G(0,1,0) | G(1,1,0) | G(2,1,0) |
| 100 | 0.953 | 0.3 | 0.954 | 0.3 | 0.955 | 0.3 | 0.959 | 0.3 | | | |
| 500 | 0.957 | 0.1 | 0.947 | 0.1 | 0.956 | 0.1 | 0.952 | 0.1 | | | |
| 10 | 0.935 | 1.0 | 0.974 | 1.0 | 0.945 | 1.1 | 0.981 | 1.0 | | | |
| 30 | 0.953 | 0.5 | 0.960 | 0.5 | 0.959 | 0.6 | 0.965 | 0.5 | 0.5N(0,1) | 0.5N(1,1) | 0.5N(2,1) |
| 100 | 0.961 | 0.3 | 0.952 | 0.3 | 0.961 | 0.3 | 0.955 | 0.3 | +0.5N(1,1) | +0.5N(2,1) | +0.5N(3,1) |
| 500 | 0.956 | 0.1 | 0.950 | 0.1 | 0.955 | 0.1 | 0.953 | 0.1 | | | |

*3.1. Discussion*

Tables 1 and 2 show the simulation results for difference of quantiles (medians) for multiple comparison to control and all pairwise comparisons respectively. Table 3 shows the simulation results for ratio of quantiles (medians) for multiple comparison to control. In Tables 1, coverage probabilities are observed to be close to the nominal 95%. AL reduces as the sample size increase. AL for $MVTq$ is on the average wider than that of the $MVNq$ irrespective of whether the CP is based on $f(\xi)$ or $\hat{f}(\hat{\xi})$. These observations are very similar to results in Table 2 and Table 3.

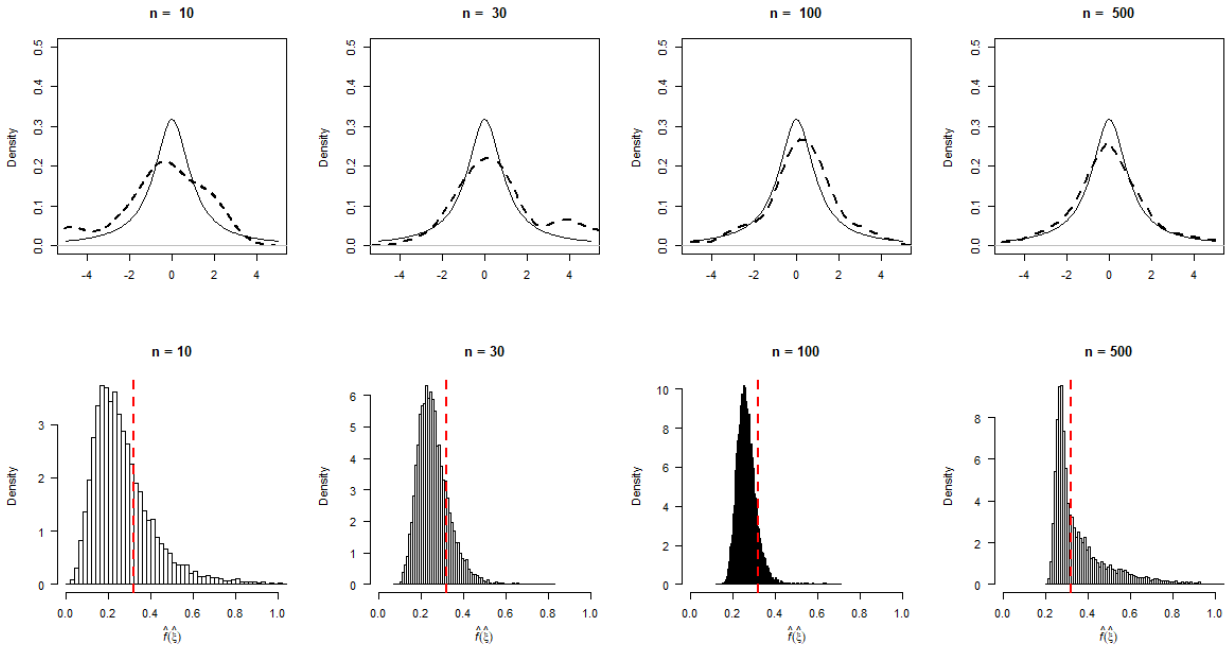


Figure 1: In the first row, true density of Cauchy(0,1) (continuous curve) and estimated densities (dashed curve) based on sample sizes $n$ are superimposed on the true density. In the second row, from 10000 replications, histograms of $\hat{f}(\hat{\xi})$ from Cauchy(0,1) varying by $n$ are shown and the vertical dashed line representing $f(\xi)$ is superimposed on each histogram.

Figure 1 and 2 show how well $\hat{f}(\hat{\xi})$ is used to estimate $f(\xi)$ for Cauchy and Laplace distributions respectively. From first row of Figure 1, the true density (continuous curve) of the cauchy distribution with mean 0 and variance 1 is under estimated by the estimated kernel density (dashed curve) at the apex. This gap is more pronounced for small $n$ with a gradual decrease as $n$ increases. The magnitude of this gap has a direct effect on the variance in (1) and $\mathbf{\Sigma}$ in the calculation of the SCIs. Large gap between $f(\xi)$ and $\hat{f}(\hat{\xi})$, where $f(\xi) > \hat{f}(\hat{\xi})$, result in a rather inflated variance and hence gives a more conservative coverage probability and vice versa. This is observed in Tables 1, 2, and 3 for the cauchy row under the columns $\hat{f}(\hat{\xi})$ for $MVNq$ and $MVTq$. This fact result from variance in (1) since $\hat{f}(\hat{\xi})$ is in the denominator.

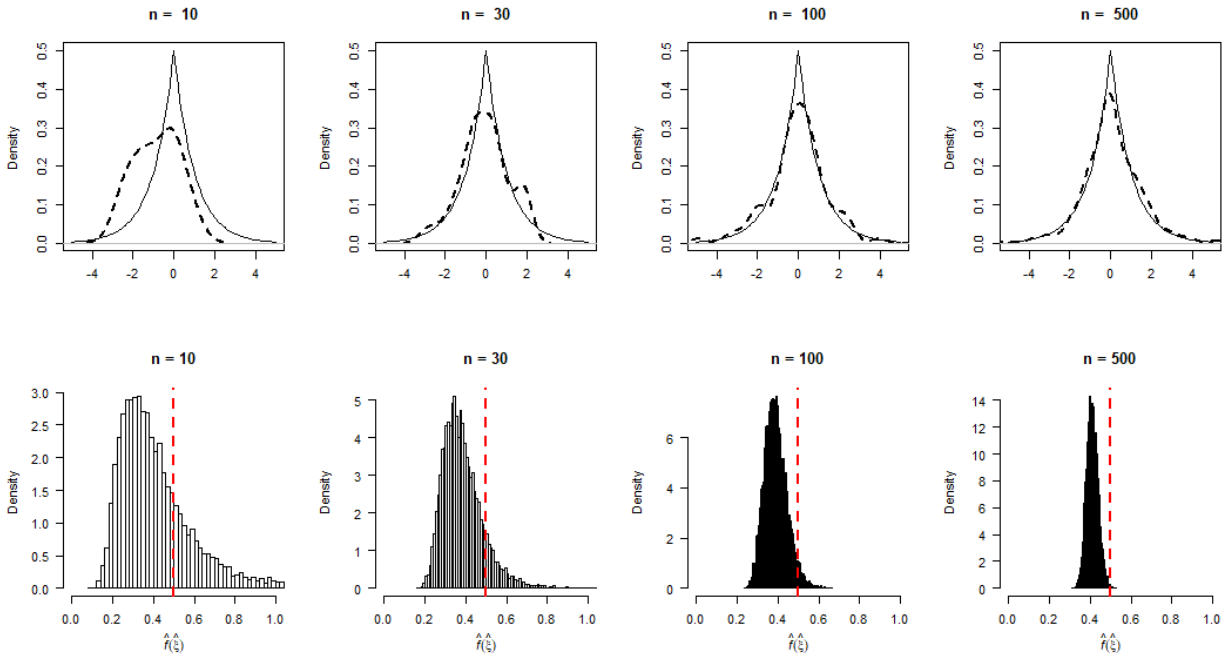


Figure 2: In the first row, true density of Laplace(0,1) (continuous curve) and estimated densities (dashed curve) based on sample sizes (n) are superimposed on the true density. In the second row, from 10000 replications, histograms of $\hat{f}(\hat{\xi})$ from Laplace(0,1) varying by sample sizes are shown and the vertical dashed line representing $f(\xi)$ is superimposed on each histogram.

The second row in Figure 1, gives an additional closer picture of how well $f(\xi)$ is estimated by $\hat{f}(\hat{\xi})$. The peak of the histograms from 10000 replications of $\hat{f}(\hat{\xi})$ is found to be lower than $f(\xi)$ (dashed vertical line). There is a direct relationship between CP under $\hat{f}(\hat{\xi})$ for Cauchy distribution in Table 1 and Figure 1. Conservative CP for $n = 10, 30, 100$ correspond with larger proportion of the histogram being lower than $f(\xi)$ (dashed vertical line). However, for $n = 500$, CP reduces because a smaller proportion of $\hat{f}(\hat{\xi})$ from 10000 overestimates $f(\xi)$ as seen in the last figure in the second row of Figure 1.

In Figure 2, the true density (continuous curve) of the Laplace distribution with mean 0 and variance 1 is under estimated by the estimated kernel density (dashed curve) at the peak. Observations discussed for Cauchy distribution in Figure 1 is similar to that of Laplace in Figure 2.

From the observations, asymptotic SCIs are conservative when $f(\xi) > \hat{f}(\hat{\xi})$ and vice versa. In other words, kernel density estimation has an influence on the coverage probability like Cauchy and Laplace distributions. Common nonparametric estimators of a probability density function show bad performance for heavy-tailed distributions (Maiborada & Markovich, 2004; Charpentier & Flachaire, 2015). Kernel density estimation is highly dependent on the bandwidth. Silverman's rule of thumb works well when data are normally distributed. The method developed by Sheather & Jones (1991) is recommended as being most reliable in terms of overall performance (Jones et al., 1996).

## 4. Application to real data

### *4.1. Example 1*

We consider an example of data originally given by Hand et. al (1994). The data consist of 57 observations of nitrogen bound bovine serum albumin in $k = 3$ groups of mice:normal mice (group 1), alloxan-induced diabetic mice (group 2), and alloxan-induced diabetic mice treated with insulin (group 3). This is a skewed data and it has been analyzed by Schaarschmidt (2012) under the assumption of lognormal distribution.

Table 4 shows a 95% asymptotic SCIs for difference of medians for the three groups of mice for multiple comparison to control based on $\hat{f}_i(\hat{\xi}_{p,i})$, $p = 0.5$. It is observed that the length of the intervals for the multivariate normal equicoordinate quantile function is smaller than the multivariate $t, df = 3(n_i - 1)$. This is also true for the simulation results in Tables 1, 2, and 3.

Table 4: A 95% SCIs for difference of medians (multiple comparison to control)

| | $MVNq$ | | $MVTq$ | |
|---|---|---|---|---|
| Comparison | Lower | Upper | Lower | Upper |
| Alloxan - Normal | -91.69 | 121.69 | -94.52 | 124.52 |
| AlloxanInsulin - Normal | -123.20 | 38.20 | -125.35 | 40.35 |

Table 5: Norminal 95% SCIs for difference of medians (All pairwise comparison)

| | $MVNq$ | | $MVTq$ | |
|---|---|---|---|---|
| Comparison | Lower | Upper | Lower | Upper |
| Alloxan - AlloxanInsulin | -39.53 | 154.53 | -42.28 | 157.28 |
| Alloxan - Normal | -97.89 | 127.89 | -101.09 | 131.09 |
| AlloxanInsulin - Normal | -127.90 | 42.90 | -130.32 | 45.32 |

*4.2. Example 2*

A typical example of skewed data is time-to-event data in survival analysis. Consider survival data from a study to determine the efficacy of boron neutron capture therapy (BNCT) in treating the therapeutically refractry F98 glioma, using boronophenylalanine (BPA) as the capture agent (Klein & Moeschberger, 2005). Three groups of rats were studied and there were 10 rats for each group. One group went untreated, another was treated with only radiation, and the third group received radiation plus an appropriate concentration of BPA. Suppose that those treated only with radiation is called the Treatment 1 and the last group which received

Table 6: Estimated survival functions ($\hat{S}$) and standard errors (in parenthesis next to $\hat{S}$) for each group in the efficacy of boron neutron capture therapy data. R and E represent the number of rats at risk and the number of events, respectively.

| Untreated | | | | Radiated | | | | Radiated+BPA | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| time | R | E | $\hat{S}$ | time | R | E | $\hat{S}$ | time | R | E | $\hat{S}$ |
| 20 | 10 | 1 | 0.9(0.0949) | 26 | 10 | 1 | 0.9(0.0949) | 31 | 10 | 1 | 0.9(0.0949) |
| 21 | 9 | 1 | 0.8(0.1265) | 28 | 9 | 1 | 0.8(0.1265) | 32 | 9 | 1 | 0.8(0.1265) |
| 23 | 8 | 1 | 0.7(0.1449) | 29 | 8 | 2 | 0.6(0.1549) | 34 | 8 | 1 | 0.7(0.1449) |
| 24 | 7 | 2 | 0.5(0.1581) | 30 | 6 | 2 | 0.4(0.1549) | 35 | 7 | 1 | 0.6(0.1549) |
| 26 | 5 | 2 | 0.3(0.1449) | 31 | 4 | 2 | 0.2(0.1265) | 36 | 6 | 1 | 0.5(0.1581) |
| 27 | 3 | 1 | 0.2(0.1265) | 32 | 2 | 1 | 0.1(0.0949) | 38 | 5 | 2 | 0.3(0.1449) |
| 28 | 2 | 1 | 0.1(0.0949) | | | | | | | | |
| 30 | 1 | 1 | 0.0 | | | | | | | | |

radiation plus BPA is called the Treatment 2. Here, the control is an untreated group. The estimated median survival times are $t_1(0.5) = 30, t_2(0.5) = 38$, and $t_C(0.5) = 25$, from the Table 6. Their corresponding standard errors are $\text{se}(t_1(0.5)) = 0.7306$, $\text{se}(t_2(0.5) = 1.5650)$ and $\text{se}t_C(0.5) = 1.2890$ by using Greenwood's formula and the presmoothed density function (Lopez-de-Ullibarri & Jacome, 2013).

Table 7 and Table 8 show 95% asymptotic SCIs for differences and ratios of median respectively for the survival data set. Both tables show the multiple comparisons to a control and all pairwise comparisons.

Table 7: Asymptotic simultaneous 95% confidence intervals for difference of medians

| | Multiple comparisons to a control | | All pairwise comparison | |
|---|---|---|---|---|
| Comparison | Lower | Upper | Lower | Upper |
| Radiaton - Radiation+BPA | - | - | -12.0301 | -3.9699 |
| Radiation - Untreated | 0.7474 | 7.2530 | 0.5593 | 7.4407 |
| Radiation+BPA - Untreated | 7.5386 | 16.4614 | 7.2811 | 16.7189 |

Table 8: Asymptotic simultaneous 95% confidence intervals for ratio of medians

| | Multiple comparisons to a control | | All pairwise comparison | |
|---|---|---|---|---|
| Comparison | Lower | Upper | Lower | Upper |
| Radiaton / Radiation+BPA | - | - | 0.7079 | 0.8857 |
| Radiation / Untreated | 1.0257 | 1.3072 | 1.0195 | 1.3191 |
| Radiation+BPA / Untreated | 1.2719 | 1.6854 | 1.2597 | 1.7026 |

## 5. Concluding remarks

In this paper, we have proposed an asymptotic method for construction SCIs for multiple contrasts of quantiles for arbitrary distributions. Many distributions of practical interest were considered in the simulation study based on the median. Coverage probabilities were observed to be close to the nominal 95% for small samples sizes and extremely skewed distribution like the exponential. Heavy tailed distribution like the Cauchy exhibited coverage probabilities that were slightly different from the nominal 95% simultaneous confidence level. Further studies would focus on the density estimation method that works best for the heavy tailed distributions.

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