

**Restricted Confidence Intervals for Ordered Binary
and Survival Data**

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Abstract

This paper considers restricted confidence intervals for binary and survival data with simple ordering. An example in a cancer clinical trial is that we expect patients with a lower stage of cancer to have higher progression free or overall survival rates at all times than those with a higher stage. This type of information is often neglected by Public Health investigators, while appropriately incorporating this information may significantly improve the efficiency in the estimators of interest. When data are normally distributed, a method has been proposed to construct restricted confidence intervals. The process is done by first identifying intermediate variables between two observations, optimizing based on the new parameter space, and then modifying the confidence interval upper and lower bounds using confidence interval limits for the intermediate random variables. In this paper, we explore and extend this method to binary data and survival data. Simulation study shows that the proposed restricted confidence intervals preserve the coverage rate well by closing to the nominal level, even when the sample size is small. The reduction of confidence interval lengths is significant when the underlying true parameters are close to each other, particularly for those with smaller sample sizes.

Keywords: Binomial distribution, Kaplan-Meier Estimator, Ordered Statistics, Restricted Confidence Interval.

Table of Contents

1.0 Introduction	1
2.0 Restricted Confidence Interval for Ordered Parameters	3
2.1 Restricted Confidence Interval for Ordered Binary Data	4
2.2 Restricted Confidence Interval for Ordered Kaplan-Meier Estimator	5
3.0 Simulation	7
3.1 Binomial Case	7
3.2 Survival Case	9
4.0 Conclusions	13
Bibliography	14

List of Tables

1	Restricted Confidence Intervals for binomial data	8
2	Restricted Confidence Intervals for survival data with $n_1 = 500$, $n_2 = 300$. .	11
3	Restricted Confidence Intervals for survival data with $n_1 = 500$, $n_2 = 50$. . .	12

1.0 Introduction

We often have information about the order of parameters of interest. For instance, if a new cancer treatment has three dose levels, $d_1 < d_2 < d_3$ and let $p_j = P(\text{Toxicity}|d_j), j = 1, 2, 3$. From biological reason, we know higher dose will cause more or at least equal toxicity than lower dose, i.e. $p_1 \leq p_2 \leq p_3$. Similarly for patients with stage 1/2 and stage 3/4 at diagnosis for a certain type of cancer, it is expected that survival probability for stage 1/2 patients is higher than that for stage 3/4 patients at all times after diagnosis. Consider G number of random variables $X_g, g = 1, \dots, G$ that are independently distributed with density function $f_g(x; \mu_g)$, when estimating the unknown parameters μ_1, \dots, μ_G , it is called simple ordering or linear ordering if there is knowledge about the order of parameters:

$$\mu_1 \leq \dots \leq \mu_G.$$

By incorporating this information in the estimation process, we can potentially obtain more efficient estimators. One natural restricted estimator is restricted maximum likelihood estimator (RMLE), which has been show to have good properties such as dominance on unrestricted MLE (Kelly, 1989; Lee, 1981). Some specialized methods for constructing restricted confidence intervals have developed (Schoenfeld, 1986; Hwang and Peddada, 1994; Peddada, 1997; Li et al., 2010). For stochastically ordered survival functions, Dykstra (1982); Dykstra and Feltz (1989); Park et al. (2012b,a) developed non-parametric estimators based on maximizing likelihood under the restriction. However, traditional inference methods, such as likelihood based method, can lead to some undesirable properties in restricted parameter space as discussed in Cohen and Sackrowitz (2004). Furthermore, the bootstrap method, a commonly used inference procedure for constructing confidence intervals of complicated parameters, will fail when a parameter is on the boundary or close to the boundary of the parameter space (Andrews, 2000).

Recently, Park et al. (2014) proposed a new method to construct restricted confidence intervals under linear ordering constraints. The proposed method is based on finding an

intermediate random variables and modifying the upper and lower limits of confidence intervals from those intermediate random variables to define restricted confidence intervals. To be specific, in two-sample situation, let $X_1 \sim N(\mu_1, \sigma_1^2)$ and $X_2 \sim N(\mu_2, \sigma_2^2)$, $\mu_1 \leq \mu_2$. We define a family of intermediate variable $X(\gamma) = \gamma X_1 + (1 - \gamma)X_2$ where γ lies between the closed interval between 0 and 1. It has been shown that the mean of $X(\gamma)$: $\mu(\gamma)$ satisfies $\mu_1 \leq \mu(\gamma) \leq \mu_2$. To minimize the variance of $X(\gamma)$, the weights are proportional to the inverse of variances of X_1 and X_2 , i.e., $\gamma = \sigma_2^2 / (\sigma_1^2 + \sigma_2^2)$. Let unrestricted confidence intervals for μ_1 , μ_2 and $\mu(\gamma)$ be $[L_1, U_1]$, $[L_2, U_2]$ and $[L(\gamma), U(\gamma)]$, then the restricted confidence intervals for μ_1 and μ_2 are defined as $[\min\{L_1, L(\gamma)\}, \min\{U_1, U(\gamma)\}]$ for μ_1 and $[\max\{L_2, L(\gamma)\}, \max\{U_2, U(\gamma)\}]$ for μ_2 . This type of restricted confidence has been shown to have desirable property with reduced average confidence widths but covering at least nominal level under normal distribution with known variances.

In this paper, we will extend Park et al. (2014)'s method to binary and survival data.

2.0 Restricted Confidence Interval for Ordered Parameters

Suppose random variables $X_g \sim N(\mu_g, \sigma_g^2)$, $g = 1, 2$, where σ_g^2 is known. To construct $1 - \alpha$ confidence intervals for μ_1 and μ_2 when it is known that $\mu_1 \leq \mu_2$, Park et al. (2014) considered a family of random variable $X(\gamma) = \gamma X_1 + (1 - \gamma)X_2$, where $\gamma \in [0, 1]$. The mean of $X(\gamma)$ are $\mu(\gamma) = EX(\gamma) = \gamma\mu_1 + (1 - \gamma)\mu_2$, which satisfies the restriction $\mu_1 \leq \mu(\gamma) \leq \mu_2$. Park et al. (2014) proposed to use the confidence interval limits from this random variable to modify the limits of the confidence interval limits for μ_1 and μ_2 . Let $z_{1-\alpha/2}$ be the upper $\alpha/2$ quantile of a standard normal distribution, which we denote for convenience by z . The unrestricted confidence intervals for μ_1 , μ_2 and $\mu(\gamma)$ are $\mu_g \in [X_g - z\sigma_g, X_g + z\sigma_g]$, $g = 1, 2$ and $\mu(\gamma) \in [X(\gamma) - z\sigma(\gamma), X(\gamma) + z\sigma(\gamma)]$, where $\sigma^2(\gamma) = \text{var}\{X(\gamma)\} = \gamma^2\sigma_1^2 + (1 - \gamma)^2\sigma_2^2$. The restricted confidence intervals $[L_1(\gamma), U_1(\gamma)]$ for μ_1 and $[L_2(\gamma), U_2(\gamma)]$ for μ_2 are:

$$\begin{aligned} L_1(\gamma) &= \min\{X_1 - z\sigma_1, X(\gamma) - z\sigma(\gamma)\}, \\ U_1(\gamma) &= \min\{X_1 + z\sigma_1, X(\gamma) + z\sigma(\gamma)\}, \end{aligned} \tag{2.1}$$

and

$$\begin{aligned} L_2(\gamma) &= \max\{X_2 - z\sigma_2, X(\gamma) - z\sigma(\gamma)\}, \\ U_2(\gamma) &= \max\{X_2 + z\sigma_2, X(\gamma) + z\sigma(\gamma)\}. \end{aligned}$$

The selection of γ is based on obtaining a more efficient restricted interval. Park et al. (2014) proposed to use $\gamma_0 = \sigma_2^2/(\sigma_1^2 + \sigma_2^2)$, which minimizes the variance of the intermediate variable $X(\gamma)$. It has been shown that the restricted confidence intervals based on γ_0 has good properties with reduced average confidence interval length for both μ_1 and μ_2 . The theoretical coverage rates are at least at nominal levels with maximum coverage rate of 0.969 for the nominal level of 0.95.

2.1 Restricted Confidence Interval for Ordered Binary Data

For binary data $X \sim \text{Bin}(n, p)$, the natural estimator for p is X/n , which is also the maximum likelihood estimator. However, there are many methods to construct confidence interval for this p , including Normal approximation interval, Wilson score interval, Jeffery's interval, Clopper–Pearson “exact” interval, Agresti–Coull interval Bootstrap interval and Arcsine transformation interval. Compared to these various methods, when we have ordering information, such as $p_1 \leq p_2$, where $X_1 \sim \text{Bin}(n_1, p_1)$ and $X_2 \sim \text{Bin}(n_2, p_2)$, the only method discussed in the literature is using bootstrapping method (Li et al., 2010). Here, we present a method to construct restricted confidence when $p_1 \leq p_2$. Following the idea in Park et al. (2014), the key is to find an appropriate intermediate random variable. Consider $X = X_1 + X_2$, it is easy to see that $p_X = E(X/n)$ satisfies $p_1 \leq p_X \leq p_2$. However, it is not easy to find the confidence interval for p_X since X follows a binomial mixture distribution. Before we propose a restricted confidence intervals, we first prove the following Theorem.

Theorem 1. *Let $X_i \sim \text{Bin}(n_i, p_i), i = 1, \dots, K$ and $Y \sim (n, p_Y)$, where $n = \sum n_i$ and $p_Y = \sum(n_i p_i) / \sum n_i$. Let $X = \sum X_i$, a binomial mixture, and $p_X = E(X/n)$, then*

$$p_X = p_Y \text{ and } \text{var}(X) \leq \text{var}(Y).$$

Proof. $p_X = E(X/n) = E(X)/n = \sum n_i p_i / n = p_Y$.

$$\text{var}(X) = \text{var}\left(\sum X_i\right) = \sum \{\text{var}(X_i)\} = \sum n_i p_i (1 - p_i).$$

Conditional on $E(X) = np_X = np_Y$, by introducing Lagrangian Multiplier, to maximize $\text{var}(X)$, it is equivalent to maximize

$$f(p_1, \dots, p_K) = \sum n_i p_i (1 - p_i) - \gamma (\sum n_i p_i - np_X),$$

conditional on $\sum n_i p_i - np_X = 0$.

$$\frac{\partial f}{\partial p_i} = n_i(1 - p_i) - n_i p_i - \gamma n_i p_i = 0,$$

We get $p_i = 1/\gamma$. This implies that $f(\cdot)$ reaches maximum when $p_1 = \dots = p_K = 1/\gamma$. Since $\sum n_i p_i - np_X = 0$, $p_i = p_X$. □

The proposed intermediate random variable is $X = X_1 + X_2$, when $p_1 \leq p_2$. The estimator is $\hat{p}_X = X/n$. Although X follows binomial mixture distribution, we construct confidence for p_X by treating $X \sim \text{Bin}(n, p_X)$. Since the variance of binomial distribution is no less than variance of binomial mixture distribution, and the length of confidence interval is approximately proportional to the square root of the variance, we expect the confidence interval region based on binomial distribution is wider than the required to achieve the nominal level. On the other hand, since confidence interval for p_X is based on $n = n_1 + n_2$ subjects, it should be more efficient than confidence intervals for p_1 and p_2 . As seen in (Park et al., 2014), the restricted confidence intervals for p_1 and p_2 by modifying the confidence limits using the confidence interval limits for p_X , we expect to gain efficiency.

Let confidence interval limits for p_1 , p_2 and p_X based on any method to construct unrestricted confidence intervals are $[L_1, U_1]$, $[L_2, U_2]$ and $[L_X, U_X]$, the restricted confidence intervals are defined as:

$$L_1^r(\gamma) = \min(L_1, L_X),$$

$$U_1^r(\gamma) = \min(U_1, U_X),$$

and

$$L_2^r(\gamma) = \max(L_2, L_X),$$

$$U_2^r(\gamma) = \max(U_2, U_X).$$

2.2 Restricted Confidence Interval for Ordered Kaplan-Meier Estimator

We often estimate the survival probability in biomedical research. For example, the survival probability of lung cancer patient at time t after diagnosis. The most commonly used nonparametric estimator is Kaplan-Meier estimator or product limit estimator (Kaplan and Meier, 1958). Let X_i be the observed time and Δ_i be the event indicator for patient i , where $\Delta_i = 1$ indicates the event and $\Delta_{gi} = 0$ indicates the censoring. The Kaplan-Meier estimator is given by

$$\hat{S}(t) = \prod_{i:t_i \leq t} \left(1 - \frac{d_i}{n_i}\right),$$

where t_i is time with at least one event; d_i is number of events; and n_i is number of patients still alive (at-risk) just prior to time t_i .

For random variables T_1 and T_2 with corresponding survival functions $S_1(t)$ and $S_2(t)$, T_2 is stochastically larger than T_1 , if $S_1(t) \leq S_2(t)$ for all t . Stochastic ordering has a wide range of applications in biomedical research. For example, in a cancer study, we expect patients with a lower stage of cancer at diagnosis to have lower death rates at all times than those with a higher stage. In the case of stochastic ordering, at each time point t , since we have order of survival function $S_1(t) \leq S_2(t)$, the pointwise interval estimation for $S_1(t)$ and $S_2(t)$ can gain efficiency if we incorporate this ordering information into the estimation procedure.

The variance of survival function is obtained using Greenwood's formula:

$$\hat{\sigma}^2(t) = \text{var}(\log(S(t))) = \sum_{i:t_i \leq t} \frac{d_i}{n_i(n_i - d_i)}.$$

Commonly used confidence interval for survival function $\log S(t)$ is given by:

$$\log \hat{S}(t) \pm z\hat{\sigma}(t),$$

which is using normal approximation of $\hat{S}(t)$ at logarithm scale.

Another commonly used transformation is called complementary log-log transformation: $\hat{T} = \log(-\log(\hat{S}(t)))$. In this transformation,

$$\hat{\sigma}_T^2 = \text{var}(\hat{T}) = \frac{\hat{\sigma}^2}{\{\log \hat{S}(t)\}^2}.$$

The confidence interval at complementary log-log transformation is:

$$\hat{T} \pm z\hat{\sigma}_T.$$

The restricted confidence intervals for $S_1(t)$ and $S_2(t)$ under condition $S_1(t) \leq S_2(t)$ is given similar to ordered normal case in (2.1) under logarithm or complementary log-log transformations. Note that the direction of the order of survival functions under complementary log-log transformation flips, since $\log(-\log(\cdot))$ is a monotonically decreasing function.

3.0 Simulation

3.1 Binomial Case

Simulations are run to compare confidence intervals and their respective coverage rates along with the interval lengths for binomial and survival data. The nominal level of confidence intervals are set to 95%.

The binomial confidence intervals are in the form of several types, including the Wald Normal Approximation, Wilson Score, Clopper-Pearson, Agresti-Coull, Jeffery, Bootstrap, and an Arcsine transformation. The sample sizes are $n_1 = 50$ and $n_2 = 100$. Data are generated from $X_i^{(b)} \sim \text{Bin}(n_i, p_i), i = 1, 2, b = 1, \dots, B$, where $p_1 = 0.50$ and $p_2 = 0.52, 0.6, 0.7, 0.8, 0.9$ respectively. The simulation results are based on $B = 1$ million replicates. As can be seen from Table 1, the restricted confidence interval generally has similar or increased coverage comparing the unrestricted counterpart. For example, the coverage for p_2 when $p_1 = 0.6$ using the Clopper-Pearson “exact” interval is 96.5 for restricted confidence interval compared to 96.5 for unrestricted one. The coverage for p_2 when $p_1 = 0.52$ using the Wilson Score Interval is 95.2 for restricted confidence interval compared to 93.5 for unrestricted one. The restricted confidence intervals are generally more efficient compared to the unrestricted counterparts. For example, the average confidence interval lengths are about 17% shorter for p_1 and 7.5% shorter for p_2 compared to unrestricted ones when $p_2 = 0.48$, which is the case when two proportions are closed to each other in our simulation, but as the p_2 departures further away from p_1 , the efficiency gain becomes smaller and smaller. When $p_2 = 0.9$, there is not noticeable changes of confidence intervals for both p_1 and p_2 . The efficiency gain of confidence interval is more for the proportion with smaller sample size (p_1) than the one with larger sample size (p_2).

Table 1: Restricted Confidence Intervals for binomial data

	$p_1 = 0.5$	$p_2 = 0.52$	$p_2 = 0.6$	$p_2 = 0.7$	$p_2 = 0.9$
<u>Normal Approximation (Wald)</u>					
Unrestricted	93.5(0.274)	94.3(0.195)	94.8(0.191)	95.0(0.179)	93.2(0.116)
Restricted	p_2	94.6(0.180)	95.0(0.186)	95.1(0.178)	93.2(0.116)
	p_1	94.6(0.226)	93.8(0.256)	93.5(0.272)	93.5(0.274)
<u>Wilson Score Interval</u>					
Unrestricted	93.5(0.265)	94.3(0.191)	94.8(0.188)	93.7(0.176)	93.6(0.118)
Restricted	p_2	94.6(0.177)	95.0(0.183)	93.8(0.175)	93.6(0.118)
	p_1	95.2(0.220)	94.0(0.249)	93.5(0.263)	93.5(0.265)
<u>Clopper-Pearson Interval</u>					
Unrestricted	96.7(0.287)	96.5(0.202)	95.9(0.199)	96.3(0.186)	95.6(0.126)
Restricted	p_2	96.5(0.186)	96.0(0.193)	96.3(0.186)	95.6(0.126)
	p_1	97.1(0.235)	96.9(0.267)	96.7(0.284)	96.7(0.287)
<u>Agresti-Coull Interval</u>					
Unrestricted	93.5(0.264)	94.3(0.191)	94.8(0.188)	95.0(0.176)	95.2(0.122)
Restricted	p_2	95.0(0.177)	95.0(0.183)	95.0(0.176)	95.2(0.122)
	p_1	95.2(0.220)	94.0(0.249)	93.5(0.263)	93.5(0.264)
<u>Jeffery Interval</u>					
Unrestricted	93.5(0.268)	94.3(0.193)	94.8(0.189)	95.0(0.177)	95.6(0.116)
Restricted	p_2	94.6(0.178)	95.0(0.184)	95.1(0.176)	95.6(0.116)
	p_1	94.6(0.222)	93.8(0.251)	93.5(0.266)	93.5(0.268)
<u>Bootstrap Interval</u>					
Unrestricted	96.7(0.279)	96.5(0.199)	95.9(0.193)	95.0(0.177)	96.6(0.114)
Restricted	p_2	96.5(0.183)	96.0(0.187)	95.1(0.177)	96.6(0.114)
	p_1	97.1(0.229)	96.9(0.260)	96.7(0.276)	96.7(0.279)
<u>Arcsine Transformation</u>					
Unrestricted	93.5(0.271)	94.3(0.194)	94.8(0.190)	95.0(0.177)	95.6(0.115)
Restricted	p_2	94.6(0.179)	95.0(0.185)	95.1(0.177)	95.6(0.115)
	p_1	94.6(0.224)	93.8(0.253)	93.5(0.269)	93.5(0.271)

Restricted Confidence Intervals for binomial data based on 1 million replicates. Sample sizes are $n_1 = 50$, $n_2 = 100$. The restriction is $p_1 \neq p_2$. The nominal level of CIs are 95%.

3.2 Survival Case

The simulations include two survival curves, $S_1(t)$ and $S_2(t)$, which follow simple ordering such that $S_1(t) \leq S_2(t)$. The data are generated from two exponential distributions with right random censoring. The simulation procedure is as follows:

1. Set $\lambda_2 = 1$ and $z = \Phi(0.975)$;
2. Select λ_1 from 1.02, 1.1 and 1.3 for $n_1 = 500$, $n_2 = 300$, or λ_1 from 1.02, 1.3 for $n_1 = 500$, $n_2 = 50$ and repeat step 3 - 12;
3. Calculate the evaluation time points: those times such that $S_1(t)$ is 0.7, 0.6, 0.5, 0.4 and 0.3 respectively;
4. Generate $t_{gi} \sim \exp(\lambda_g)$, $g = 1, i = 1, \dots, n_g$;
5. Generate $c_{gi} \sim U(0, 3)$;
6. Make survival data as: $x_{gi} = \min(t_{gi}, c_{gi})$, $\Delta_i = (t_{gi} \leq c_{gi})$;
7. Fit survfit using R with data (x_{gi}, Δ_{gi}) ;
8. Obtain unrestricted confidence interval at each evaluation time point for both $S_1(t)$ and $S_2(t)$ under logarithm and complementary log-log transformations;
9. Obtain confidence intervals of intermediate random variables under under both transformations;
10. Obtain restricted confidence intervals for $S_1(t)$ and $S_2(t)$ under both transformations;
11. Repeat Steps 3 - 10 for 10,000 times;
12. Obtain coverage rate and averages lengths of confidences at each evaluation time points under both transformations.

When sample sizes on both groups are relatively large (Table 2), the coverage of restricted confidence intervals are very close to the nominal levels (95%) in all scenarios and at all time points. It is expected as the sample size is large, central limit theorem ensures that the good normal approximation as this type of restricted confidence intervals has been shown to have good properties in normal distribution cases (Park et al., 2014). The restricted confidence intervals are more efficient when $S_1(t)$ and $S_2(t)$ are close to each other (the case with $\lambda_1 = 1.02$ in Table 2) with about 10% and 17% reduction of average lengths for $S_1(t)$

and $S_2(t)$ respectively. When $S_1(t)$ and $S_2(t)$ are far from each other as seen when $\lambda_1 = 1.3$ in Table 2), there is no noticeable gains of efficiency by using restricted confidence intervals. The over-coverage of restricted confidence discussed in Park et al. (2014), such that the restricted confidence interval has at least nominal level or better coverage than unrestricted counterpart, does not seem to hold for log transformation in some situations. This may be an indication that the complementary log-log transformation converges to normal distribution faster than log transformation when using Kalpan-Meier estimator.

We also explore when sample sizes are small and are very different. In table 3, we consider when $n_1 = 500$ and $n_2 = 50$. In this situation, the restricted confidence interval for $S_2(t)$ gains a big efficiency by reducing 25% of average length when two survival functions are close to each other ($\lambda_2 = 1.02$). Even when $S_1(t)$ and $S_2(t)$ are not very close ($\lambda_2 = 1.3$), we still see a noticeable efficiency gain (15% reduction of average length). So the estimation for more variable parameters ($S_2(t)$ in this simulation) is benefiting more from the restricted method. We also notice that complementary log-log transformation is better than log transformation in terms of producing confidence intervals with coverage closer to the nominal levels in most of the cases we considered. So we suggest to use complementary log-log transformation when applying our method to constructed restricted confidence interval.

Table 2: Restricted Confidence Intervals for survival data with $n_1 = 500$, $n = 300$

$\lambda = 1.02$	$S_1(t)$	0.7	0.6	0.5	0.4	0.3
$\lambda = 1$	$S_2(t)$	0.705	0.606	0.507	0.407	0.307
			<u>log transformation</u>			
Unrestricted	$S_1(t)$	94.8(0.083)	94.9(0.090)	94.9(0.094)	95.2(0.095)	94.7(0.093)
	$S_2(t)$	94.6(0.107)	94.6(0.116)	95.2(0.121)	95.2(0.123)	94.6(0.121)
Restricted	$S_1(t)$	95.4(0.075)	95.4(0.082)	95.6(0.085)	96.0(0.086)	95.4(0.084)
	$S_2(t)$	94.5(0.088)	94.7(0.097)	95.1(0.101)	95.5(0.104)	94.6(0.103)
			<u>complementary log-log</u>			
Unrestricted	$S_1(t)$	95.0(0.083)	94.9(0.090)	94.9(0.094)	95.2(0.095)	94.8(0.093)
	$S_2(t)$	95.3(0.106)	95.2(0.115)	95.2(0.121)	94.9(0.123)	94.8(0.121)
Restricted	$S_1(t)$	95.1(0.077)	95.0(0.083)	95.9(0.087)	95.2(0.088)	95.8(0.085)
	$S_2(t)$	97.0(0.090)	96.9(0.100)	97.2(0.106)	98.0(0.108)	96.9(0.108)
$\lambda = 1.1$	$S_1(t)$	0.7	0.6	0.5	0.4	0.3
$\lambda = 1$	$S_2(t)$	0.723	0.629	0.533	0.435	0.335
			<u>log transformation</u>			
Unrestricted	$S_1(t)$	94.5(0.083)	94.7(0.090)	94.8(0.094)	95.0(0.094)	95.0(0.092)
	$S_2(t)$	94.8(0.104)	94.6(0.114)	94.8(0.120)	94.6(0.123)	94.9(0.122)
Restricted	$S_1(t)$	95.2(0.078)	95.2(0.085)	95.2(0.089)	95.3(0.090)	95.4(0.087)
	$S_2(t)$	95.3(0.093)	95.1(0.104)	95.3(0.110)	95.2(0.114)	95.5(0.113)
			<u>complementary log-log</u>			
Unrestricted	$S_1(t)$	94.6(0.083)	94.6(0.090)	94.8(0.094)	95.2(0.094)	94.8(0.093)
	$S_2(t)$	95.1(0.103)	95.0(0.114)	94.9(0.120)	94.7(0.123)	95.0(0.122)
Restricted	$S_1(t)$	95.2(0.078)	95.1(0.085)	95.1(0.089)	95.5(0.090)	95.2(0.087)
	$S_2(t)$	95.7(0.093)	95.7(0.104)	95.7(0.110)	95.3(0.114)	95.7(0.138)
$\lambda = 1.3$	$S_1(t)$	0.7	0.6	0.5	0.4	0.3
$\lambda = 1$	$S_2(t)$	0.760	0.675	0.587	0.494	0.396
			<u>log transformation</u>			
Unrestricted	$S_1(t)$	95.3(0.082)	95.1(0.089)	95.2(0.093)	95.0(0.093)	95.0(0.090)
	$S_2(t)$	94.4(0.099)	94.6(0.110)	94.6(0.117)	94.5(0.122)	94.8(0.122)
Restricted	$S_1(t)$	95.3(0.082)	95.1(0.089)	95.2(0.092)	95.0(0.092)	95.0(0.089)
	$S_2(t)$	94.9(0.097)	94.6(0.109)	94.6(0.117)	94.5(0.121)	94.8(0.122)
			<u>complementary log-log</u>			
Unrestricted	$S_1(t)$	95.3(0.082)	95.0(0.089)	95.2(0.092)	95.1(0.092)	95.0(0.089)
	$S_2(t)$	94.0(0.099)	94.9(0.110)	94.6(0.117)	94.8(0.121)	94.7(0.122)
Restricted	$S_1(t)$	95.3(0.082)	95.0(0.089)	95.2(0.092)	95.1(0.092)	95.0(0.089)
	$S_2(t)$	95.0(0.097)	94.9(0.108)	94.6(0.116)	94.8(0.120)	94.7(0.121)

Restricted Confidence Intervals (%) for survival data based on 10,000 replicates. Sample sizes are $n_1 = 500$, $n_2 = 300$. Event data are generated using exponential distribution with rate λ_1 and λ_2 . λ_2 is set to 1 while λ_1 is 1.02, 1.1 and 1.3 respectively. Censoring data are generated from $U(0, 3)$. The restriction $S_1(t) < S_2(t)$ is satisfied for all $t > 0$. The nominal level of CIs are 95%. The evaluation t is selected for $S_1(t) = 0, 7, 0.6, 0.5, 0.4, 0.3$ respectively. Numbers in parentheses are average length of the confidence intervals.

Table 3: Restricted Confidence Intervals for survival data with $n_1 = 500$, $n_2 = 50$

$\lambda = 1.02$	$S_1(t)$	0.7	0.6	0.5	0.4	0.3
$\lambda = 1$	$S_2(t)$	0.705	0.606	0.507	0.407	0.307
		log transformation				
Unrestricted	$S_1(t)$	95.0(0.083)	94.9(0.090)	95.1(0.094)	95.3(0.095)	95.2(0.093)
	$S_2(t)$	93.3(0.259)	93.9(0.284)	94.3(0.298)	94.4(0.305)	95.0(0.304)
Restricted	$S_1(t)$	95.2(0.081)	95.1(0.088)	95.3(0.092)	95.5(0.093)	95.3(0.091)
	$S_2(t)$	92.2(0.179)	93.1(0.200)	93.5(0.216)	93.8(0.226)	94.2(0.232)
		complementary log-log				
Unrestricted	$S_1(t)$	95.1(0.083)	94.9(0.090)	95.2(0.094)	95.5(0.095)	95.2(0.092)
	$S_2(t)$	95.2(0.259)	95.0(0.279)	94.8(0.289)	95.3(0.290)	95.2(0.283)
Restricted	$S_1(t)$	95.0(0.081)	94.9(0.088)	95.3(0.092)	95.5(0.092)	95.2(0.090)
	$S_2(t)$	96.8(0.154)	96.7(0.174)	96.6(0.188)	96.7(0.195)	96.6(0.198)
$\lambda = 1.3$	$S_1(t)$	0.7	0.6	0.5	0.4	0.3
$\lambda = 1$	$S_2(t)$	0.712	0.615	0.517	0.418	0.318
		log transformation				
Unrestricted	$S_1(t)$	94.9(0.118)	95.0(0.150)	95.0(0.188)	95.1(0.237)	94.9(0.308)
	$S_2(t)$	92.8(0.148)	93.8(0.188)	94.4(0.235)	94.2(0.295)	94.8(0.382)
Restricted	$S_1(t)$	95.1(0.110)	95.1(0.140)	95.1(0.175)	95.2(0.222)	95.0(0.305)
	$S_2(t)$	92.8(0.125)	93.8(0.159)	94.4(0.200)	94.2(0.252)	94.8(0.237)
		complementary log-log				
Unrestricted	$S_1(t)$	95.1(0.082)	95.1(0.089)	95.1(0.093)	95.1(0.093)	95.1(0.090)
	$S_2(t)$	95.3(0.242)	95.3(0.266)	95.6(0.281)	95.1(0.290)	95.2(0.290)
Restricted	$S_1(t)$	95.2(0.082)	95.1(0.089)	95.1(0.092)	95.0(0.092)	95.1(0.089)
	$S_2(t)$	95.4(0.186)	95.3(0.215)	95.6(0.236)	95.1(0.251)	95.2(0.256)

Restricted Confidence Intervals (%) for survival data based on 10,000 replicates. Sample sizes are $n_1 = 500$, $n_2 = 50$. Event data are generated using exponential distribution with rate λ_1 and λ_2 . λ_2 is set to 1 while λ_1 is 1.02 and 1.3 respectively. Censoring data are generated from $U(0, 3)$. The restriction $S_1(t) < S_2(t)$ is satisfied for all $t > 0$. The nominal level of CIs are 95%. The evaluation t is selected for $S_1(t) = 0, 7, 0.6, 0.5, 0.4, 0.3$ respectively. Numbers in parentheses are average length of the confidence intervals.

4.0 Conclusions

In this paper, we presented restricted confidence intervals for binary and survival data when order of the parameters exists. The strategy is to find an intermediate random variable and using the confidence interval limits from this intermediate random variable to obtain the restricted confidence interval limits for the original ordered parameters. This is an extension of Park et al. (2014) from Gaussian data to binary and survival data.

The advantage of our method is that there are as many forms of restricted confidence intervals as those of unrestricted ones. In binomial situation, we showed that we can treat the binomial mixture as binomial distribution with the same mean in constructing restricted confidence intervals. Simulation study shows that the restricted confidence intervals can preserve accurate coverage rate with gained efficiency by reducing average confidence interval lengths up to 27% when two parameters are close to each other.

The data above were simulated only comparing two groups. This method is easily able to be extended to data containing multiple groups following the strategy from Park et al. (2014). The discoveries regarding the increased coverage and efficiency of the confidence intervals should be applicable to situations with more than two groups since the confidence intervals for a group can be constructed by depending on the data for that group and its adjacent neighbor only. While this is an option, it may be more efficient to combine groups rather than estimating on just the closest group, but there may be scientific or study-specific barriers preventing that.

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