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CONFIDENCE SETS-BASED PROCEDURES FOR IDENTIFYING THE MINIMUM EFFECTIVE DOSE WITH RIGHT-CENSORED LIFETIME DATA

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ABSTRACT

In this paper, we consider identifying the minimum effective dose (MED) in a dose-response study with randomly right-censored lifetime data, where the MED is the lowest dose level with a median lifetime larger than that of the zero-dose control by a certain threshold value. The MED is identified based on the stepwise confidence sets for the ratios of median lifetimes of each non-zero dose group and the zero-dose control. Parametric confidence sets are proposed when lifetimes in different dose groups are distributed as generalized gamma distributions. Nonparametric confidence sets are also suggested when distributions of the lifetimes remain unknown. The comparative results of a Monte Carlo error rate and power/bias study for a variety of survival and censoring distributions are then presented and discussed. The application of the proposed procedures is finally illustrated for identifying the MED of the diethylstilbestrol in the treatment of prostate cancer.

Key words and phrases: Confidence set, generalized gamma distribution, median lifetime, minimum effective dose, right-censored data.
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1. Introduction

In animal experiments or clinical trials for drug development, dose-response studies are frequently conducted to evaluate the treatment effects of the drug under study. In such studies, subjects or patients are usually randomly allocated to different groups to receive either the placebo (or zero-dose) or a variety of dose levels of the drug. One factor of interest in these studies is to identify the minimum effective dose (MED) of the drug, where the MED is defined to be the smallest dose level producing a clinically important response that can be declared statistically significantly more effective than the placebo response (Ruberg, 1995).

Under the assumption that responses are normally distributed with a common variance, Ruberg (1989) proposed single-step multiple tests based on different contrasts of sample means to identify the MED. Tamhane et al. (1996) suggested use of contrast-based closed testing procedures for identifying the MED which is more powerful than the single-step multiple tests. However, when the assumption of normal distribution is not tenable, Chen (1999) identified the MED using the step-down closed testing procedure incorporated with the Mann-Whitney statistics.

Alternative to closed testing procedures, Hsu and Berger (1999) suggested identification of the MED based on step-down confidence sets for the differences in normal means between each treatment group and the control group with a specified threshold value for the mean differences. Bretz et al. (2003) further identified the MED by constructing step-down confidence sets for the ratios of the normal means of each treatment group and the control group. Notice that the confidence sets-based approaches not only generate meaningful guarantee against incorrect decision for the MED identification, but also provide with confidence lower bounds for the efficacy of the dose levels lower than the identified MED relative to the zero-dose control.

In fact, in animal experiments or clinical trials, it occurs quite often that the end point of interest is time to tumor occurrence or the prolonged lifetime of subjects with a particular disease. Moreover, since the study may be terminated at a pre-assigned time owing to time limitation, or the patients may be lost to follow-up randomly, the lifetime data are frequently subject to random right-censorship. Therefore, Chen

and Chang (2007a) suggested step-down testing procedures based on different types of weighted logrank statistics for identifying the MED. In the testing procedures, hazard functions are of primary interest and zero is the threshold value for the difference between two hazard functions. However, in clinical trials involving lifetime data, the median lifetime, which serves as a clinically meaningful parameter, is much easier than the hazard function for the interpretation of the drug-efficacy under study. Therefore, in this paper, we consider to identify the MED based on the ratio of the median lifetimes in each non-zero dose treatment group and the zero-dose control group.

Notice that the generalized gamma distribution (Stacy, 1962 and Cox et al., 2007) includes, in particular, the lognormal, gamma and Weibull distributions and a variety of right-skewed distributions. Therefore, we construct lower confidence bounds for the ratios of interest when the lifetime data in different groups are distributed according to possibly different generalized gamma distributions. Moreover, Chen and Chang (2007b) proposed covariate-dependent confidence interval for the ratio of two median lifetimes. When the continuous distributions of the lifetimes under study are unknown, we consider employing the lower confidence bound in the Chen-Chang (2007b) confidence interval for the ratio without any covariates. Finally, we identify the MED by applying the step-down procedure proposed by Hsu and Berger (1999) along with appropriate lower confidence bounds for the median ratios.

In Section 2, we introduce the problem under study and review the step-down procedure in Hsu and Berger (1999). In Section 3, we propose two methods for identifying the MED based on different kinds of confidence sets. One kind of confidence sets is developed under the assumption of generalized gamma distributions for the lifetimes under study and the other kind is a special procedure obtained from Chen and Chang (2007b). The results of a Monte Carlo study investigation of the relative experimentwise error rate and power/bias performances of the competing procedures are presented and discussed in Section 4. The use of these testing procedures is then illustrated in Section 5 with the numerical example involving the prostate cancer data (Byar and Corle, 1977). Finally, in Section 6, we give a discussion on the application of the proposed testing procedures.

2. Data, problem and step-down testing procedure

Suppose that the zero population ($i = 0$) is the zero-dose control and the other k populations correspond to the increasing dose levels. Let $\{(T_{ij}, C_{ij}), j = 1, \ldots, n_i\}$ be the lifetime and censoring time of size n_i in group i, $i = 0, 1, \ldots, k$. Furthermore, assume that the $k + 1$ samples are independent of each other and the censoring time C_{ij} is distributed independently of the lifetime T_{ij}. In this setting, we observe the $k+1$ groups of data, $\{(Y_{ij}, \delta_{ij}), j = 1, \ldots, n_i\}$, $i = 0, 1, \ldots, k$, where $Y_{ij} = \min(T_{ij}, C_{ij})$ and $\delta_{ij} = I(T_{ij} \leq C_{ij})$. Let $S_i(t)$ be the survivor function of the lifetime in group i and then the associated median lifetime is

$$\xi_i = \sup\{t : S_i(t) \geq 0.5\}, i = 0, 1, \ldots, k.$$

Let $\Delta_i = \xi_i/\xi_0$ be the ratio of medians, or median-ratio, for $i = 1, \ldots, k$. In this paper, we consider identifying the MED defined as

$$\text{MED} = \min\{i : \Delta_i > \Delta, i = 1, \ldots, k\}. \tag{1}$$

where $\Delta \geq 1$ is the threshold value indicating a clinically significant difference in median lifetimes.

To identify the MED, we implement the step-down procedure in Hsu and Berger (1999) for testing the null hypothesis $H_{0i} : \Delta_i \leq \Delta$ against the alternative hypothesis $H_{Ai} : \Delta_i > \Delta$, for $i = 1, \ldots, k$. To do so, we need to construct the lower confidence bound for Δ_i for $i = 1, \ldots, k$, which will be discussed in the next two sections. In this section, we briefly review the Hsu-Berger (1999) procedure.

Let LCB_i be the $100(1 - \alpha)\%$ lower confidence bound for Δ_i, $i = 1, \ldots, k$. The step-down procedure starts, at the first step, with testing against H_{Ak} by comparing the kth non-zero dose group with the zero-dose control. If $LCB_k \geq \Delta$, then we claim $\Delta_k > \Delta$ and the testing procedure proceeds to the second step for testing against $H_{A(k-1)}$; otherwise, the procedure is stopped and we conclude that the MED is beyond the dose levels under study. In this case, the identified MED is labeled to be $k + 1$. When the procedure comes to testing for $H_{0(k-m+1)}$ at the mth step, $1 \leq m \leq k$, we then claim $\Delta_{k-m+1} > \Delta$ if $LCB_{k-m+1} \geq \Delta$ and continue the testing procedure for

$m < k$; otherwise, we stop the testing procedure and identify MED to be $k - m + 2$ for $m < k$, but claim MED to be the first dose level under study when $m = k$. In fact, when the MED is identified to be j^*, we conclude that $\Delta_j^* > \Delta, \ldots, \Delta_k > \Delta$ and assure that, with $100(1-\alpha)\%$ confidence level, $\Delta_j \geq LCB_j$ for $j = 1, \ldots, j^* - 1$ with $j^* \geq 2$.

3. The proposed methods

3.1 Parametric approach

Suppose that the lifetime variables in group i $(i = 0, 1, \ldots, k)$ are distributed as different generalized gamma distributions (Stacy, 1962 and Cox et al., 2007) with the probability density function:

$$f(t; \beta_i, \sigma_i, \lambda_i) = \begin{cases} \frac{|\lambda_i|}{\sigma_i t \Gamma(\lambda_i^{-2})} \left\{ \lambda_i^{-2} (e^{-\beta_i} t)^{\lambda_i/\sigma_i} \right\}^{\lambda_i^{-2}} \exp\left\{ -\lambda_i^{-2} (e^{-\beta_i} t)^{\lambda_i/\sigma_i} \right\} & \text{for } \lambda_i \neq 0 \\ \frac{1}{\sigma_i t \sqrt{2\pi}} \exp\left\{ -(\log t - \beta_i)^2 / 2\sigma_i^2 \right\} & \text{for } \lambda_i = 0, \end{cases} \tag{2}$$

where β_i, σ_i and λ_i are the location, scale and shape parameters, respectively, for group i $(i = 0, 1, \ldots, k)$. We denote such a generalized gamma distribution, hereafter, by $GG(\beta_i, \sigma_i, \lambda_i)$. The associated survivor function is then given as follows:

$$S(t; \beta_i, \sigma_i, \lambda_i) = \begin{cases} 1 - \Gamma(\lambda_i^{-2} (e^{-\beta_i} t)^{\lambda_i/\sigma_i}; \lambda_i^{-2}) & \text{for } \lambda_i > 0 \\ \Gamma(\lambda_i^{-2} (e^{-\beta_i} t)^{\lambda_i/\sigma_i}; \lambda_i^{-2}) & \text{for } \lambda_i < 0 \\ 1 - \Phi((\log t - \beta_i)/\sigma_i) & \text{for } \lambda_i = 0, \end{cases} \tag{3}$$

where $\Gamma(t; \gamma) = \int_0^t x^{\gamma-1} e^{-x} dx / \Gamma(\gamma)$ is the distribution function for the gamma random variable with mean and variance both equal to γ, and $\Phi(\cdot)$ is the distribution function of a standard normal random variable.

Notice that the median lifetime of the $GG(\beta_i, \sigma_i, \lambda_i)$ can be solved by setting $S_i(t) = 0.50$ for $i = 0, 1, \ldots, k$. Let $\Gamma^{-1}(p; \gamma)$ denote the $100p$th percentile of the gamma distribution with mean and variance both equal to γ. Then, the associated median lifetime is obtained as

$$\xi_i = e^{\beta_i} (m_{\lambda_i})^{\sigma_i} \quad \text{for} \quad i = 0, 1, \ldots, k,$$

where

$$m_{\lambda_i} = \begin{cases} \left[\lambda_i^2 \Gamma^{-1}(0.5; \lambda_i^{-2}) \right]^{1/\lambda_i} & \text{for } \lambda_i \neq 0 \\ 1 & \text{for } \lambda_i = 0 \end{cases} \tag{4}$$

is the median lifetime of the gamma distribution with mean and variance equal to λ_i^{-2}, which can be easily solved by using the subroutine *qgamma* in *R* package. Hence, the natural logarithm of the median lifetime for $GG(\beta_i, \sigma_i, \lambda_i)$ can be written as

$$\log(\xi_i) = \beta_i + \sigma_i \log(m_{\lambda_i}) \quad \text{for} \quad i = 0, 1, \ldots, k,$$

and the natural logarithm of the median-ratio is given by

$$\log(\Delta_i) = \log(\xi_i) - \log(\xi_0) = \beta_i - \beta_0 + \sigma_i \log(m_{\lambda_i}) - \sigma_0 \log(m_{\lambda_0}),$$

where m_{λ_i} is stated in (4) for $i = 0, 1, \ldots, k$.

Notice that, following the work in Cox et al. (2007), we obtain the MLEs of β_i, σ_i and λ_i, denoted by $\hat{\beta}_i$, $\hat{\sigma}_i$ and $\hat{\lambda}_i$, respectively, for $i = 0, 1, \ldots, k$, by maximizing the likelihood function of β_i, σ_i and λ_i based on the observed right-censored data in group i:

$$L(\beta_i, \sigma_i, \lambda_i) = \prod_{j=1}^{n_i} \{f(y_{ij}; \beta_i, \sigma_i, \lambda_i)\}^{\delta_{ij}} \{S(y_{ij}; \beta_i, \sigma_i, \lambda_i)\}^{1-\delta_{ij}},$$

where $f(y_{ij}; \beta_i, \sigma_i, \lambda_i)$ and $S(y_{ij}; \beta_i, \sigma_i, \lambda_i)$ are specified in (2) and (3), respectively. Moreover, taking the inverse of the observed Fisher information matrix, we find the variance-covariance matrices of the random vectors, $(\hat{\beta}_i, \hat{\sigma}_i, \hat{\lambda}_i)$ and $(\hat{\beta}_0, \hat{\sigma}_0, \hat{\lambda}_0)$, as denoted by $\mathbf{\Sigma}_i$ and $\mathbf{\Sigma}_0$, respectively. Then, the logarithm of the median-ratio can be estimated by

$$\log(\hat{\Delta}_i) = \hat{\beta}_i - \hat{\beta}_0 + \hat{\sigma}_i \log(m_{\hat{\lambda}_i}) - \hat{\sigma}_0 \log(m_{\hat{\lambda}_0}) \quad \text{for} \quad i = 1, \ldots, k.$$

Applying the Delta method, we further obtain the standard error of $\log(\hat{\Delta}_i)$ as given by

$$se(\log \hat{\Delta}_i) = (\mathbf{x}_0^t \mathbf{\Sigma}_0 \mathbf{x}_0 + \mathbf{x}_i^t \mathbf{\Sigma}_i \mathbf{x}_i)^{1/2}, \ i = 1, \ldots, k,$$

where $\mathbf{x}_i = (1, \log(m_{\hat{\lambda}_i}), \hat{\sigma}_i \partial m_{\hat{\lambda}_i} / \partial \hat{\lambda}_i)^t$ and $\mathbf{a}^t$ is the transpose of $\mathbf{a}$. Notice that $\partial m_{\hat{\lambda}_i} / \partial \hat{\lambda}_i$ can be evaluated by using the subroutine *g*rad in the *R* package. Therefore, a $100(1-\alpha)\%$ lower confidence bound for Δ_i is obtained as

$$LCB_i = \hat{\Delta}_i \exp\left\{-z_{1-\alpha} se(\log \hat{\Delta}_i)\right\}, \ i = 1, \ldots, k. \tag{5}$$

where $z_{1-\alpha}$ is the $100(1-\alpha)$th percentile of a standard normal distribution. Hence, we suggest use of the step-down testing procedure in Section 2 based on the k parametric lower confidence bounds (5) to identify the MED.

Notice that, to use the proposed lower confidence bounds in (5) for the MED identification, we need to perform a goodness-of-fit test for the generalized gamma distribution. Herein, we suggest one use the modified Kolmogorov's test statistic as given by

$$KM = sup\{|\hat{S}(t) - \tilde{S}(t)|\},$$

where $\hat{S}(t)$ is the Kaplan-Meier (1958) estimate and $\tilde{S}(t) = S(t; \hat{\beta}, \hat{\sigma}, \hat{\lambda})$ is the estimated survivor function under the generalized gamma distribution. Let km be the observed value of KM. Then, the associated p-value is given by

$$p - value = P\{KM \geq km | GG(\beta, \sigma, \lambda)\},$$

Therefore, we claim that the generalized gamma distribution is not feasible for the data if $p - value \leq \alpha$. Notice that an approximated p-value can be found by using the bootstrap procedure stated in the following:

Step 1. Generate a random sample from the original data set.

Step 2. Find $\hat{S}(t)$ and $\tilde{S}(t)$ based on the bootstrap sample obtained in Step 1.

Step 3. Repeat Step 1 and Step 2 B times and obtain $\hat{S}_b(t)$ and $\tilde{S}_b(t)$ for $b = 1, \ldots, B$.

Step 4. Compute $KM_b = sup\{|\hat{S}_b(t) - \tilde{S}_b(t)|\}$ for $b = 1, \ldots, B$.

Step 5. Compute $p - value \approx \sum_{b=1}^{B} I(KM_b \geq km)/B$

3.2 Nonparametric approach

Let $\hat{S}_i(t)$ be the Kaplan-Meier estimate for the survivor function in group i at time t. Then, the associated median lifetime ξ_i can be estimated by

$$\hat{\xi}_i = \sup\{t : \hat{S}_i(t) \geq 0.5\}, i = 0, 1, \ldots, k.$$

To avoid directly finding the sampling distribution of the $(\hat{\xi}_i/\hat{\xi}_0)$'s, Chen and Chang (2007b) considered the minimum-quadratic dispersion statistic (Basawa and Koul, 1988) as follows:

$$Q(\hat{\Delta}_i) = \min_{\xi_0} W(\hat{\Delta}_i, \xi_0),$$

where

$$W(\tilde{\Delta}_i, \xi_0) = \frac{\{\hat{S}_0(\xi_0) - 0.5\}^2}{\hat{\sigma}_0^2(\xi_0)} + \frac{\{\hat{S}_i(\tilde{\Delta}_i\xi_0) - 0.5\}^2}{\hat{\sigma}_i^2(\tilde{\Delta}_i\xi_0)}. \tag{6}$$

and $\hat{\sigma}_i^2(t)$ is the Greenwood's (1926) formula for $\hat{S}_i(t), i = 0, 1, \ldots, k$. Since the test statistic $Q(\tilde{\Delta}_i)$ is asymptotically chi-square distributed with one degree of freedom, denoted by χ_1^2, Chen and Chang (2007b) then obtain, by inverting the quantity $Q(\tilde{\Delta}_i)$, a $100(1-2\alpha)\%$ confidence set CI_i for Δ_i in the following:

$$CI_i = \{\tilde{\Delta}_i : Q(\tilde{\Delta}_i) < \chi_1^2(2\alpha)\},\ i = 1, \ldots, k, \tag{7}$$

where $\chi_1^2(2\alpha)$ is the upper 200αth percentile of χ_1^2. Notice that the lower bound of the $100(1-2\alpha)\%$ CI_i in (7) gives a $100(1-\alpha)\%$ lower confidence bound, LCB_i, for Δ_i, $i = 1, \ldots, k$. Therefore, the MED can be identified, again, according to the step-down testing procedure described in Section 2, but, based on the k nonparametric lower confidence bounds.

In fact, the quadratic dispersion statistic considered in Su and Wei (1993) is

$$W_{sw}(\tilde{\Delta}_i, \xi_0) = \frac{\{\hat{S}_0(\xi_0) - 0.5\}^2}{\hat{\sigma}_0^2(\hat{\xi}_0)} + \frac{\{\hat{S}_i(\tilde{\Delta}_i\xi_0) - 0.5\}^2}{\hat{\sigma}_i^2(\hat{\xi}_i)},\ i = 1, \ldots, k, \tag{8}$$

where the Greenwood's (1926) formulas are both evaluated, for simplicity, at the estimated median lifetimes. Therefore, the confidence interval considered in Chen and Chang (2007b) is, in fact, a modification of the Su-Wei (1993) procedure. Moreover, the simulation results in Chen and Chang (2007b) demonstrate that the original Su-Wei procedure gives a more conservative confidence interval for the median-ratio in the two-sample problem. Hence, we suggest one use the nonparametric lower confidence bounds from the modified Su-Wei procedure for the MED identification.

4. A simulation study

We conducted a Monte Carlo study to examine the relative error rate, power and bias performances of the parametric and nonparametric testing procedures considered in this paper, denoted by GG and MSW, respectively. The error rate performances of the testing procedures were evaluated by the experimentwise error rate (EWE, the probability of incorrectly declaring MED under the global null hypothesis) and family-wise error rate (FWE, the probability of underestimating the MED). The probability of correctly identifying the MED and $\{E(\widehat{\text{MED}}) - \text{MED}\}$, respectively, were then used to assess the power and bias performances of the testing procedures. We consider $k = 3$ treatments with sample sizes $n_0 = n_1 = \ldots = n_k = n = 30$ and 50 in the EWE study, and $n = 30$ in the FWE and power/bias study.

A variety of generalized gamma distributions were taken as the lifetime distributions. To investigate how the parametric procedure behaves when the lifetime variable is not distributed to the generalized gamma, we also considered the log-logistic distribution for the lifetime variable with survivor function $S(t; \beta, \lambda) = 1/(1 + \beta t^{\lambda})$ for $t > 0$, where β and λ are the scale and shape parameters, respectively. The uniform distribution over $(0, r)$ was then used as the censoring distribution. In the EWE study, the common lifetime distribution for each group is the generalized gamma distribution $GG(\beta, \sigma, \lambda)$ with $\beta = 0.5$, $\sigma = 1.0$ or 1.5, and $\lambda = -1.0, 0.0$ or 1.0. The log-logistic distribution under study in the EWE study has $\beta = 0.5$ or 2.0 and $\lambda = 0.8$ or 1.2. In the EWE study, we chose r=10 or 20, which correspond to the censoring probability ranging from 7% to 45%. However, for simplicity, we only considered the uniform censoring distribution with r=20 in the FWE and power/bias study.

In the FWE and power/bias study, we consider, specifically, five major cases for the parameter-configurations and distributions. The first four cases involve the generalized gamma distributions that have various values of β_i, $i = 0, 1, \ldots, k$, but specified scale and shape parameters as follows:

I. $\sigma = 1.5,\ \lambda = -1.0.$

II. $\sigma = 1.5,\ \lambda = 0.0.$

III. $\sigma = 1.5,\ \lambda = 1.0.$

IV. $\sigma = 1.0,\ \lambda = -1.0.$

The last case is the log-logistic distribution with

V. $\lambda = 0.8$ and various values of β_i, $i = 0, 1, \ldots, k$.

Notice that cases II and III correspond to the lognormal and Weibull distributions, respectively, while cases I and IV are referred as the inverse Weibull distribution.

For each of these settings, 10,000 replicates were used to obtain the estimated EWE, FWE, power, and bias under the nominal level $\alpha = 0.05$ as reported in Tables 1 and 2. Notice that the maximum standard error for the error rate and power estimators is about $0.005(\approx \sqrt{(0.5)(0.5)/10,000})$. In fact, the standard deviation of the error rate estimator is about $0.002(\approx \sqrt{(0.5)(0.95)/10,000})$. Also, notice that, when the true MED is one, the FWE is zero since no type I error is involved. Therefore, we leave the FWE blank for the situation with MED=1 in Table 2.

It is evident, upon examination of the results in Table 1, that the parametric procedure GG maintains its EWE well under the generalized gamma distributions. However, under the log-logistic distribution, the GG tends to be conservative in holding its EWE. Nevertheless, the nonparametric procedure MSW reasonably maintains its EWE when the lifetime is distributed to either the generalized gamma or log-logistic distribution.

The results in Table 2 confirm that the FWE of the parametric and nonparametric procedures are both under control. Moreover, it is not surprising to find that the power of the parametric procedure GG is larger than that of the nonparametric procedure MSW for the generalized gamma distributions under cases I-IV. In these cases, the bias of GG is smaller than that of MSW. However, the MSW is superior to GG for the log-logistic distributions under case V in terms of both the power and bias. This is because the log-logistic distribution is not a member of the generalized gamma distribution for which the parametric procedure GG is specifically designed.

Table 1 Estimated experimentwise error rates for α =0.05, $n_0 = n_1 = n_2 = n_3 = n$ with uniform censoring distribution $U(0, \mathrm{r})$

				r = 10		r = 20	
β	σ	λ	n	GG	MSW	GG	MSW
Generalized gamma distribution							
0.5	1.0	-1.0	30	0.048	0.053	0.054	0.050
			50	0.051	0.051	0.052	0.047
0.5	1.5	-1.0	30	0.056	0.048	0.055	0.047
			50	0.048	0.046	0.049	0.045
0.5	1.0	0.0	30	0.052	0.050	0.054	0.046
			50	0.049	0.045	0.053	0.045
0.5	1.5	0.0	30	0.054	0.049	0.054	0.048
			50	0.048	0.044	0.052	0.047
0.5	1.0	1.0	30	0.049	0.051	0.049	0.051
			50	0.054	0.046	0.053	0.045
0.5	1.5	1.0	30	0.050	0.050	0.047	0.047
			50	0.055	0.048	0.051	0.047
Log-logistic distribution							
0.5		0.8	30	0.043	0.050	0.033	0.050
			50	0.032	0.046	0.034	0.045
2.0		0.8	30	0.029	0.047	0.032	0.048
			50	0.043	0.047	0.036	0.045
0.5		1.2	30	0.035	0.051	0.039	0.048
			50	0.037	0.048	0.040	0.048
2.0		1.2	30	0.036	0.046	0.033	0.047
			50	0.041	0.045	0.038	0.045

5. Data analysis

The data from a randomized and double-blinded clinical trial involving patients with prostate cancer (Byar and Corle, 1977) were used for illustration. There were 81 patients of stage IV with tumor of size greater than 20 cm^2, but without evidence of distant metastasis, in which 21 took the placebo pill and served as the control group, 17 received 0.2 mg of diethylstilbestrol (DES) as dosage group 1, 23 were treated with

Table 2 Estimated FWE, power and bias for α =0.05, $n_0 = n_1 = n_2 = n_3 = n$ with uniform censoring distribution $U(0, 20)$

					FWE		Power		Bias	
β_0	β_1	β_2	β_3	MED	GG	MSW	GG	MSW	GG	MSW
I. σ =1.5, λ = -1.0										
0.5	0.5	0.5	2.0	3	0.054	0.048	0.764	0.737	0.065	0.156
0.5	0.5	2.0	2.0	2	0.054	0.049	0.666	0.647	0.373	0.461
0.5	2.0	2.0	2.0	1	—	—	0.666	0.633	0.832	0.890
0.5	0.5	1.0	2.0	2	0.050	0.030	0.249	0.183	0.818	0.976
0.5	1.0	1.5	2.0	1	—	—	0.254	0.183	1.371	1.538
II. σ =1.5, λ = 0.0										
0.5	0.5	0.5	2.0	3	0.051	0.052	0.886	0.854	-0.015	0.028
0.5	0.5	2.0	2.0	2	0.056	0.049	0.845	0.797	0.103	0.197
0.5	2.0	2.0	2.0	1	—	—	0.837	0.793	0.307	0.463
0.5	0.5	1.0	2.0	2	0.043	0.033	0.275	0.229	0.712	0.796
0.5	1.0	1.5	2.0	1	—	—	0.252	0.217	1.071	1.268
III. σ =1.5, λ = 1.0										
0.5	0.5	0.5	2.0	3	0.056	0.045	0.815	0.774	0.054	0.126
0.5	0.5	2.0	2.0	2	0.052	0.045	0.718	0.662	0.304	0.422
0.5	2.0	2.0	2.0	1	—	—	0.708	0.622	0.696	0.845
0.5	0.5	1.0	2.0	2	0.039	0.025	0.208	0.175	0.836	0.954
0.5	1.0	1.5	2.0	1	—	—	0.194	0.160	1.400	1.545
IV. σ =1.0, λ = -1.0										
0.5	0.5	0.5	2.0	3	0.054	0.052	0.938	0.926	-0.072	-0.043
0.5	0.5	2.0	2.0	2	0.057	0.050	0.933	0.913	-0.052	0.011
0.5	2.0	2.0	2.0	1	—	—	0.977	0.952	0.050	0.108
0.5	0.5	1.0	2.0	2	0.050	0.043	0.410	0.336	0.478	0.602
0.5	1.0	1.5	2.0	1	—	—	0.455	0.368	0.659	0.834
V. Log-logistic, λ = 0.8										
0.5	0.5	0.5	0.1	3	0.047	0.051	0.744	0.798	0.148	0.089
0.5	0.5	0.1	0.1	2	0.047	0.049	0.634	0.706	0.478	0.358
0.5	0.1	0.1	0.1	1	—	—	0.604	0.693	0.921	0.718
0.5	0.5	0.2	0.1	2	0.044	0.042	0.423	0.432	0.695	0.634
0.5	0.3	0.2	0.1	1	—	—	0.184	0.186	1.552	1.491

1.0 mg of DES as dosage group 2 and 20 were assigned to take 5.0 mg of DES as dosage group 3. Patients were followed according to a standard protocol at 6-month interval or more frequently if required, and the lifetimes of the patients in the four groups since

randomization were recorded. For patients who had not yet died or were dead due to causes other than the prostate cancer, the observed times were regarded as censored data. Herein, we are concerned with the MED of DES under study so that the median lifetime of the involved patients is larger than that of the patients taking the placebo pill by a threshold value of Δ. The Kaplan-Meier estimates of the survivor functions for the four groups were shown in Figure 1. Moreover, by inverting directly from these Kaplan-Meier estimates, the median lifetimes can be estimated to be 28, 21, 37 and 56 months for the four dosage groups, respectively.

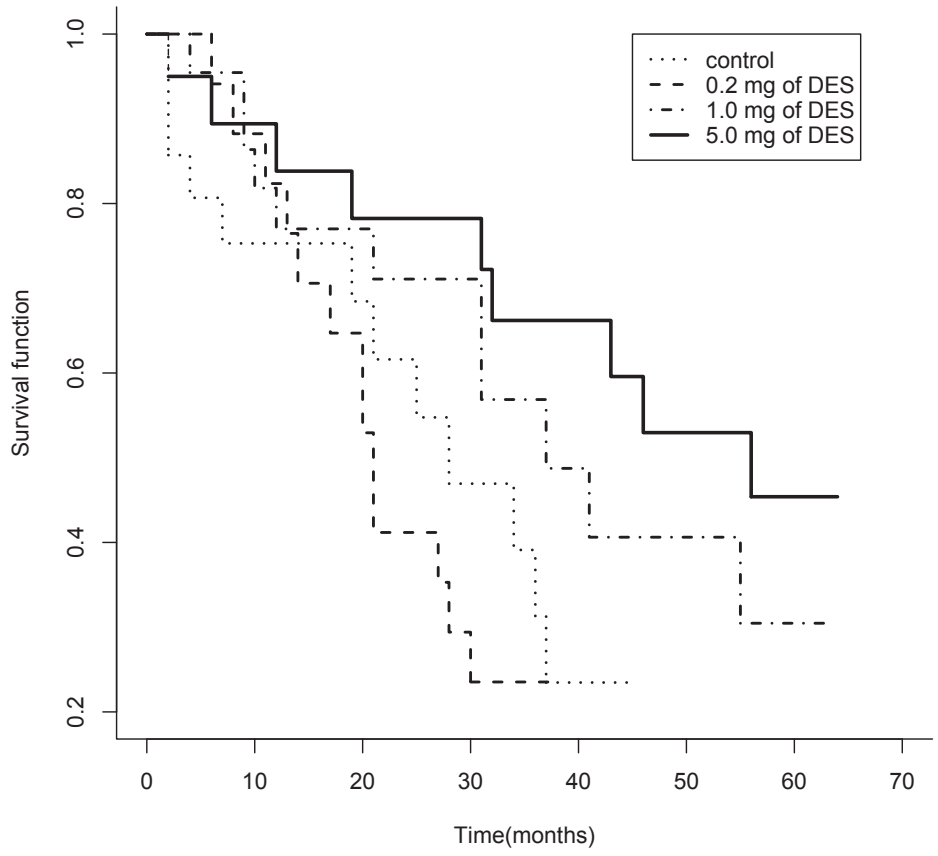

Figure 1 The Kaplan-Meier estimates for the prostate cancer data.

We obtain the 95% lower confidence bounds for the ratios of the medians in each of treatment groups and the zero-dose control group based on the data with or without

the assumption of the generalized gamma distributions. Notice that, based on 1,000 bootstrap samples, the modified Kolmogorov test suggested in Section 3 give p-values of 0.482, 0.598, 0.136 and 0.647 for the four groups of data. Therefore, the generalized gamma distributions seem to be plausible for describing the distributions of the four groups of data under study. In fact, the results in Table 3 indicate that, for the threshold value one, both the parametric GG and nonparametric MSW methods identify the MED to be 5.0 mg of DES. In other words, only the group of patients administered with 5.0 mg of DES has a median lifetime longer than the zero-dose control group. However, for any threshold value between 1.130 and 1.143, only the suggested MSW procedure concludes that the 5.0 mg of DES is the MED of interest. In this case, the MSW procedure further assures that, under 95 percent confidence level, the median lifetimes of the 1.0 mg and 0.2 mg of DES groups are at least 0.861 and 0.500 times, respectively, greater than that of the zero-dose control. Finally, we conjecture that the reason why the MSW procedure is more powerful than the parametric procedure is perhaps that the modified Kolmogorov test gives a slightly evidence against the generalized gamma distribution for the third group of data.

Table 3 The 95% lower confidence bounds for the ratios of median lifetimes for the prostate cancer data.

	GG	MSW	SW
5.0 mg vs. control	1.130	1.143	0.941
1.0 mg vs. control	0.759	0.861	0.861
0.2 mg vs. control	0.484	0.500	0.500

In fact, based on the original Su-Wei (1993) procedure, denoted by SW, we found the related 95 percent lower confidence bounds for the median-ratio of the three non-zero dosage groups relative to the zero-dose control are 0.941, 0.861 and 0.500, respectively. Therefore, the MED identification procedure based on the original Su-Wei (1993) lower confidence bounds would lead to the conclusion that the MED of the DES in the treatment of the prostatic patients is beyond the largest dosage under study. This is not surprising since the original Su-Wei (1993) procedure gives a more conservative confidence bound for the median-ratio than the modified one considered in Chen and

Chang (2007b).

6. Conclusions and remarks

In this paper, we discuss how to identify the minimum effective dose (MED) in a clinical trial based on the step-down testing procedure suggested in Hsu and Berger (1999) when lifetime data are subject to random right-censorship. To do so, we derive parametric confidence set for the ratio of medians for each treatment dose group and the control group under generalized gamma distributions. We also employ the nonparametric confidence set obtained from Chen and Chang (2007b). Therefore, the two procedures would fulfill the need for MED identification for a variety of practical situations.

As demonstrated in the simulation, both the parametric and nonparametric procedures perform reasonably under the generalized gamma distributions. However, when the underlying populations are not generalized gamma distributed, the parametric procedure tends to be conservative. To choose an appropriate procedure for use on the MED identification, we suggest one use the modified Kolmogorov test for the goodness-of-fit of the generalized gamma distribution for each treatment group. If the generalized gamma distribution is feasible for all the groups of data, then the parametric procedure is recommended; otherwise, the nonparametric procedure is suggested.

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