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UMBRELLA TESTS FOR RIGHT-CENSORED SURVIVAL DATA

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Abstract: This paper considers the problem of testing for umbrella alternatives in the one-way layout when survival data are subject to random right censorship. Testing procedures based on two-sample weighted logrank statistics are suggested for both cases when the peak of the umbrella is known or unknown. The Pitman efficacy of the peak-known umbrella test is derived. A class of Lehmann and scale alternatives for which the peak-known umbrella test is optimal in the sense of Pitman efficacy is then obtained under the assumption of equal censorship. Moreover, the results of a Monte Carlo study to investigate the level and power performances of the proposed umbrella tests are presented. Finally, application of the proposed procedures to an appropriate data set is illustrated.

Key words and phrases: Monte Carlo study, one-way layout, Pitman efficacy, right-censored data, umbrella alternatives.

1. Introduction

Dose-response studies are frequently used to assess the relative treatment effects of increasing dose levels of a substance in animal experiments or clinical trials, where the response of interest is, for instance, time to tumor occurrence or the prolonged survival time of patients with a particular disease. These studies may lead to randomly right-censored data, since they may be terminated at preassigned times, subjects who randomly enter a study may be lost to follow-up randomly, or death may be due to a competing risk which is not of interest.

For the ith sample ($i = 1, \ldots, k$), let $T_{i1}, ..., T_{in_i}$ be independent and identically distributed (i.i.d.) random variables each with a continuous distribution function F_i, and let $C_{i1}, \ldots, C_{in_i}$ be i.i.d. random variables each with a continuous distribution function G_i, where C_{ij} is the censoring time associated with the survival time T_{ij}. Suppose that the k samples are mutually independent and that the T_{ij} and C_{ij} are also mutually independent. In such a setting, we actually observe only X_{ij} =minimum$\{T_{ij}, C_{ij}\}$ and the indicator of censorship $\delta_{ij} = I\{T_{ij} \leq C_{ij}\}$, $j = 1, \ldots, n_i$, $i = 1, \ldots, k$. Let $S_i = 1 - F_i$, $i = 1, \ldots, k$. When increasing dose levels may lead to a larger or at least equal efficacy, Liu, Green, Wolf and Crowley (1993) proposed a generalization of the Jonckheere (1954)-Terpstra (1952) test for $H_0 : (S_1 = \cdots = S_k)$ against the ordered alternatives $H_{1O} : (S_1 \leq \cdots \leq S_k$, with at least one strict inequality) (Barlow, Bartholomew, Bremner and Brunk (1972)) based on two-sample weighted logrank statistics.

However, monotonicity of dose-response relationships is far from universal. For example, medical therapies often become counter-productive at high doses. In such cases, an increasing dose-response relationship with a downturn in response at high doses is anticipated. The corresponding up-down ordering of the treatment effects is referred to as an umbrella pattern (Mack and Wolfe (1981)) and the point that separates the treatment effects into the two different ordering groups is called the peak of the umbrella. In this paper we are concerned with testing procedures against the umbrella alternative $H_{1U} : (S_1 \leq \cdots \leq S_p \geq \cdots \geq S_k$, for some p, with at least one strict inequality) when randomly right-censored data are involved.

In Section 2 we propose a generalization of the Mack-Wolfe (1981) test for peak-known umbrella alternatives based on the two-sample weighted logrank statistics. Two special cases are investigated in detail: the umbrella version of logrank test (Mantel (1966)), and the umbrella Peto-Prentice-Wilcoxon test (Peto and Peto (1972), Prentice (1978)). In Section 3 the Pitman efficacy for the peak-known umbrella tests is derived. The class of Lehmann and scale umbrella alternatives, for which the peak-known umbrella tests are optimal in the sense of Pitman efficacy, is then obtained. In Section 4 a generalized Chen-Wolfe (1990) test is suggested for peak-unknown umbrella alternatives with censored data. Section 5 contains a numerical example and in Section 6 we present the results of a simulation investigation of the level and power performances of the proposed tests for a variety of umbrella pattern treatment effects configurations. The final section contains some suggestions for future work.

2. Peak-Known Umbrella Test

Define, for $j = 1, \ldots, n_i$, $i = 1, \ldots, k$, simple counting processes $D_{ij}(t) = I\{X_{ij} \leq t, \delta_{ij} = 1\}$ with associated at-risk processes $Y_{ij}(t) = I\{X_{ij} > t\}$. Let $D_i(t) = \sum_{j=1}^{n_i} D_{ij}(t)$ and $Y_i(t) = \sum_{j=1}^{n_i} Y_{ij}(t)$ for $i = 1, \ldots, k$. Using the counting process formulation, the two-sample weighted logrank statistic for testing $H_0 : S_1 = S_2$ against $H_1 : S_1 < S_2$ with right-censored data is written as

$$U = \int W(t) \frac{Y_1(t)Y_2(t)}{Y_1(t) + Y_2(t)} \Big\{ \frac{dD_1(t)}{Y_1(t)} - \frac{dD_2(t)}{Y_2(t)} \Big\}, \tag{2.1}$$

where $\int$ denotes the integration from zero to infinity. Harrington and Fleming (1982) suggested use of $W(t) = \{\hat{S}(t-)\}^{\rho}\{1-\hat{S}(t-)\}^{\gamma}$ for $\rho, \gamma \geq 0$, where $\hat{S}(t-)$ is the Kaplan-Meier (1958) survival estimate based on the pooled samples from populations 1 and 2. Note that taking $\rho = \gamma = 0$ produces the logrank statistic and setting $\rho = 1$ and $\gamma = 0$ yields the Peto-Prentice-Wilcoxon statistic. Let $M_{ij}(t) = D_{ij}(t) - \int_0^t Y_{ij}(s)d\Lambda_i(s)$ and $M_i(t) = \sum_{j=1}^{n_i} M_{ij}(t) = D_i(t) - \int_0^t Y_i(s)d\Lambda_i(s)$, where $\Lambda_i(s)$ is the cumulative hazard function for T_{ij} for $j = 1, \ldots, n_i$, $i = 1, \ldots, k$. According to the martingale-based analysis of censored data established by Aalen (1978) and Gill (1980), the two-sample weighted logrank statistic can also be written as

$$U = \int V_1(t)dM_1(t) - \int V_2(t)dM_2(t) + \int K(t)d\{\Lambda_1(t) - \Lambda_2(t)\}, \qquad (2.2)$$

where $K(t) = W(t)Y_1(t)Y_2(t)/[Y_1(t) + Y_2(t)]$ and $V_i(t) = K(t)/Y_i(t)$, $i = 1, 2$. Suppose that, as $n_1 + n_2 \to \infty$, $Y_i(t)/n_i \xrightarrow{p} \pi_i(t)$, uniformly in t, $i = 1, 2$. Applying the Martingale Central Limit Theorem (see, for example, Theorem 6.2.1 in Fleming and Harrington (1991)), it can be seen that, under H_0,

$$(n_1 + n_2)^{-1/2} U \xrightarrow{d} N(0, \sigma^2),$$

where $\sigma^2 = \int [\nu_1(t) + \nu_2(t)][1 - \Delta\Lambda(t)]d\Lambda(t)$, $\nu_i(t)$ is the limit of $V_i^2(t)Y_i(t)/(n_1 + n_2)$, $i = 1, 2$, and $\Delta\Lambda(t) = \Lambda(t) - \Lambda(t-)$. A consistent estimate of σ^2 (see, for example, Lemma 4.3.1 in Gill (1980)) is then given by $\hat{\text{Var}}\,(U)/(n_1 + n_2)$, where

$$\hat{\text{Var}}\,(U) = \int [V_1^2(t)Y_1(t) + V_2^2(t)Y_2(t)]\Big\{1 - \frac{\Delta D_1(t) + \Delta D_2(t) - 1}{Y_1(t) + Y_2(t) - 1}\Big\} \frac{d[D_1(t) + D_2(t)]}{Y_1(t) + Y_2(t)},$$

with $\Delta D_i(t) = D_i(t) - D_i(t-)$, $i = 1, 2$. So, a two-sample weighted logrank test is obtained which rejects H_0 in favor of H_1 if $U/\sqrt{\hat{\text{Var}}\,(U)} \geq z(\alpha)$, where $z(\alpha)$ is the upper αth percentile of a standard normal distribution. Note that, as $n_1 + n_2 \to \infty$, if $W(t) \xrightarrow{p} w(t)$, then $(n_1 + n_2)^{-1} K(t) \xrightarrow{p} w(t)\lambda_1\lambda_2\pi_1(t)\pi_2(t)/[\lambda_1\pi_1(t) + \lambda_2\pi_2(t)]$. Suppose that, under the stochastic ordering alternative $H_1 : S_1(t) < S_2(t)$ for all t,

$$\int w(t) \frac{\lambda_1\lambda_2\pi_1(t)\pi_2(t)}{\lambda_1\pi_1(t) + \lambda_2\pi_2(t)} d\{\Lambda_1(t) - \Lambda_2(t)\} > 0.$$

Then

$$(n_1 + n_2)^{-1/2} \int K(t)d\{\Lambda_1(t) - \Lambda_2(t)\} \xrightarrow{p} \infty, \quad \text{as } n_1 + n_2 \to \infty.$$

Hence, the two-sample weighted logrank test is consistent under the stochastic ordering alternative (see, for example, Theorem 7.3.2 in Fleming and Harrington (1991)).

When the peak of the umbrella alternative, p, is known, and we have right-censored data, we consider a generalization of the Mack-Wolfe (1981) umbrella test statistic, namely,

$$A_p = \sum_{i=2}^{p} U_i^{(1)} + \sum_{j=p}^{k-1} U_j^{(2)}, \qquad (2.3)$$

where $U_i^{(1)}$ is the two-sample weighted logrank statistic comparing the ith sample with the combined samples of 1 through $i-1$, and $U_j^{(2)}$ is the two-sample weighted logrank statistic comparing the jth sample with the combined samples of $j+1$ through k. In the rest of the paper, for simplicity, the notation (t) in all the functions of time t will be deleted. Let $D_i^{(1)} = \sum_{u=1}^{i} D_u$, $Y_i^{(1)} = \sum_{u=1}^{i} Y_u$, $D_j^{(2)} = \sum_{v=j}^{k} D_v$ and $Y_j^{(2)} = \sum_{v=j}^{k} Y_v$ for $i, j = 1, \ldots, k$. Since the $U_i^{(1)}$ and $U_j^{(2)}$ are two-sample weighted logrank statistics, from (2.1) they can be expressed as

$$U_i^{(1)} = \int W_i^{(1)} \frac{Y_i Y_{i-1}^{(1)}}{Y_i^{(1)}} \Big\{ \frac{dD_{i-1}^{(1)}}{Y_{i-1}^{(1)}} - \frac{dD_i}{Y_i} \Big\}, \qquad i = 2, \ldots, p$$

and

$$U_j^{(2)} = \int W_j^{(2)} \frac{Y_j Y_{j+1}^{(2)}}{Y_j^{(2)}} \Big\{ \frac{dD_{j+1}^{(2)}}{Y_{j+1}^{(2)}} - \frac{dD_j}{Y_j} \Big\}, \qquad j = p, \ldots, k-1$$

where $W_i^{(1)}$ and $W_j^{(2)}$ are the weight functions based on the first i samples and the last $(k-j+1)$ samples, respectively. Recalling the independent zero-mean martingales $M_i = D_i - \int Y_i d\Lambda_i$, $i = 1, \ldots, k$, the $U_i^{(1)}$ and $U_j^{(2)}$ can also be expressed as

$$\begin{aligned} U_i^{(1)} &= \int W_i^{(1)} \frac{Y_i}{Y_i^{(1)}} d \sum_{u=1}^{i-1} M_u - \int W_i^{(1)} \frac{Y_{i-1}^{(1)}}{Y_i^{(1)}} dM_i \\ &\quad + \int W_i^{(1)} \frac{Y_i Y_{i-1}^{(1)}}{Y_i^{(1)}} \Big\{ \frac{\sum_{u=1}^{i-1} Y_u d\Lambda_u}{Y_{i-1}^{(1)}} - d\Lambda_i \Big\}, \ i = 2, \ldots, p \end{aligned} \tag{2.4}$$

and

$$\begin{aligned} U_j^{(2)} &= \int W_j^{(2)} \frac{Y_j}{Y_j^{(2)}} d \sum_{u=j+1}^{k} M_u - \int W_j^{(2)} \frac{Y_{j+1}^{(2)}}{Y_j^{(2)}} dM_j \\ &\quad + \int W_j^{(2)} \frac{Y_j Y_{j+1}^{(2)}}{Y_j^{(2)}} \Big\{ \frac{\sum_{u=j+1}^{k} Y_u d\Lambda_u}{Y_{j+1}^{(2)}} - d\Lambda_j \Big\}, \ j = p, \ldots, k-1. \end{aligned} \tag{2.5}$$

Introducing the $U_i^{(1)}$ and $U_j^{(2)}$ in (2.4) and (2.5), respectively, into (2.3), we have, after some algebraic manipulation,

$$A_p = \sum_{i=1}^{k} \int V_i^{(p)} dM_i + \sum_{i=1}^{k} \int K_i^{(p)} d\Lambda_i, \tag{2.6}$$

where, for $i = 1, \ldots, k$,

$$V_i^{(p)} = \begin{cases} \sum_{u=i+1}^{p} \{W_u^{(1)} Y_u / Y_u^{(1)}\} - W_i^{(1)} Y_{i-1}^{(1)} / Y_i^{(1)}, & \text{if } 1 \le i \le p-1, \\ -W_p^{(1)} Y_{p-1}^{(1)} / Y_p^{(1)} - W_p^{(2)} Y_{p+1}^{(2)} / Y_p^{(2)}, & \text{if } i = p, \\ \sum_{u=p}^{i-1} \{W_u^{(2)} Y_u / Y_u^{(2)}\} - W_i^{(2)} Y_{i+1}^{(2)} / Y_i^{(2)}, & \text{if } p+1 \le i \le k, \end{cases} \tag{2.7}$$

and $K_i^{(p)} = V_i^{(p)} Y_i$, with $Y_0^{(1)} = Y_{k+1}^{(2)} = 0$. Let $N = \sum_{i=1}^k n_i$. Since $\text{Var}\,(M_i) = E\{Y_i(1-\Delta\Lambda)d\Lambda\}$, $i = 1, \ldots, k$, according to properties of the martingales (see, for instance, Corollary 2.3.2 and Theorem 2.4.4 in Fleming and Harrington (1991)), we have, under H_0,

$$\text{Var}\,(A_p) = \sum_{i=1}^{k} E \int \{V_i^{(p)}\}^2 Y_i (1 - \Delta\Lambda) d\Lambda.$$

Suppose that, as $N \to \infty$, $Y_i/n_i \xrightarrow{p} \pi_i$ for $i = 1, \ldots, k$. We observe

$$\{V_i^{(p)}\}^2 Y_i / N \xrightarrow{p} \nu_i^{(p)}, \quad \text{for } i = 1, \ldots, k, \tag{2.8}$$

where the $\nu_i^{(p)}$ are nonnegative, left continuous with right-hand limits, and

$$\sigma_p^2 = \sum_{i=1}^{k} \int \nu_i^{(p)} (1 - \Delta\Lambda) d\Lambda < \infty. \tag{2.9}$$

As an extension of Corollary 7.2.1 in Fleming and Harrington (1991), we obtain that, under H_0,

$$N^{-1/2} A_p \xrightarrow{d} N(0, \sigma_p^2), \quad \text{as } N \to \infty.$$

An appealing estimator of σ_p^2 is then given by $\hat{\text{Var}}\,,(A_p)/N$, where

$$\hat{\text{Var}}\,(A_p) = \sum_{i=1}^{k} \int \{V_i^{(p)}\}^2 Y_i \Big\{1 - \frac{\Delta D - 1}{Y - 1}\Big\} \frac{dD}{Y} \tag{2.10}$$

with $Y = \sum_{i=1}^k Y_i$, $D = \sum_{i=1}^k D_i$ and $\Delta D(t) = D(t) - D(t-)$. In fact, it can be verified, along the lines of the proof of Lemma 4.3.1 (Gill (1980)), that $\hat{\text{Var}}\,(A_p)/N$ provides a consistent estimator of σ_p^2.

Note that large values of $U_i^{(1)}$ in (2.3) indicate that the survival time of the ith group is longer than that of the previous combined groups $\{1, \ldots, i-1\}$. Similarly, large values of $U_j^{(2)}$ provide evidence for the better survival of the jth group than that of the following combined groups $\{j+1, \ldots, k\}$. Therefore, we propose the umbrella test which rejects H_0 in favor of $H_{1U}^p : (S_1 \leq \cdots \leq S_p \geq \cdots \geq S_k$ with at least one strict inequality) if

$$A_p^* = A_p \Big/ \sqrt{\hat{\text{Var}}\,(A_p)} \geq z(\alpha), \tag{2.11}$$

where $z(\alpha)$ is, again, the upper αth percentile of a standard normal distribution. If, as $N \to \infty$, the weight functions employed in the $U_i^{(1)}$ and $U_j^{(2)}$ in (2.4) and (2.5), respectively, converge in probability to $w(\cdot)$ or w, then $K_i^{(p)}/N \xrightarrow{p} \kappa_i^{(p)}$, where

$$\frac{\kappa_i^{(p)}}{w\lambda_i\pi_i} = \begin{cases} \sum_{u=i+1}^{p} \left\{\lambda_u\pi_u \Big/ \sum_{s=1}^{u} \lambda_s\pi_s\right\} - \sum_{u=1}^{i-1} \lambda_u\pi_u \Big/ \sum_{s=1}^{i} \lambda_s\pi_s, & \text{if } 1 \leq i \leq p-1, \\ -\sum_{u=1}^{p-1} \lambda_u\pi_u \Big/ \sum_{s=1}^{p} \lambda_s\pi_s - \sum_{u=p+1}^{k} \lambda_u\pi_u \Big/ \sum_{s=p}^{k} \lambda_s\pi_s, & \text{if } i = p, \\ \sum_{u=p}^{i-1} \left\{\lambda_u\pi_u \Big/ \sum_{s=1}^{k} \lambda_s\pi_s\right\} - \sum_{u=i+1}^{k} \lambda_u\pi_u \Big/ \sum_{s=i}^{k} \lambda_s\pi_s, & \text{if } p+1 \leq i \leq k. \end{cases} \tag{2.12}$$

Suppose that, under the stochastic ordering alternative $H_{1U}^p : (S_1 \leq \cdots \leq S_p \geq \cdots \geq S_k$, with at least one strict inequality), $\sum_{i=1}^k \int \kappa_i^{(p)} d\Lambda_i > 0$. We then observe that $N^{-1/2} \sum_{i=1}^k \int K_i^{(p)} d\Lambda_i \xrightarrow{p} \infty$, as $N \to \infty$. Therefore, the test based on A_p^* at (2.11) is consistent under H_{1U}.

Remark 1. When the survivals of the treatment groups are expected to decrease up to a certain point and then increase with further doses, the umbrella alternative with increasing dosages of interest is $H_{2U}^p : (S_1 \geq \cdots \geq S_p \leq \cdots \leq S_k$, with at least one strict inequality). For this setting, we suggest rejection of H_0 in favor of H_{2U}^p if

$$A_p^* = A_p \Big/ \sqrt{\hat{\text{Var}}\,(A_p)} \leq -z(\alpha),$$

Note that the ordered test proposed in Liu, Green, Wolf and Crowley (1993) compares the statistic $(A_1^*)^2$ with the upper αth percentile of a chi-squared distribution with one degree of freedom. This ordered test is, in fact, suitable for testing against the alternative hypothesis $H_1 : (S_1 \leq \cdots \leq S_k$ or $S_1 \geq \cdots \geq S_k$, each with at least one strict inequality).

3. Asymptotic Relative Efficiency for the Peak-Known Setting

Consider contiguous alternatives, where the absolutely continuous distribution functions F_{Ni} can depend on N and $\sup_{0 \leq t \leq \infty} |F_{Ni}(t) - F(t)| \to 0$ as $N \to \infty$, $i = 1, \ldots, k$, for some absolutely continuous distribution function F. Let $\Lambda_{Ni}(t)$ be the cumulative hazard function associated with $F_{Ni}(t)$. Suppose that

$\sqrt{N}\{d\Lambda_{Ni}/d\Lambda - 1\} \to \gamma_i$ and $\int |\gamma_i| d\Lambda < \infty$ for $i = 1, \ldots, k$. Note that, under the contiguous alternatives, the mean of $N^{-1/2}A_p$ (see (2.6)) is $\mu = \sum_{i=1}^k \int \kappa_i^{(p)} \gamma_i d\Lambda$, where the $\kappa_i^{(p)}$ are given in (2.12). Moreover, the Martingale Central Limit Theorem implies $N^{-1/2}A_p \xrightarrow{d} N(\mu, \sigma_p^2)$, as $N \to \infty$, where σ_p^2 is stated in (2.9). Since the test based on the statistic A_p^* is consistent under H_{1U}, the statistic with the higher power against H_{1U} should have the large value of the parameter $|\sum_{i=1}^k \int \kappa_i^{(p)} \gamma_i d\Lambda| / \{\sigma_p^2\}^{1/2}$. Therefore, the Pitman efficacy of the test based on A_p^* is given by

$$e(A_p^*) = \frac{\left\{\sum_{i=1}^k \int \kappa_i^{(p)} \gamma_i d\Lambda\right\}^2}{\sigma_p^2}. \tag{3.1}$$

Let $\lambda_i^{(1)} = \sum_{u=1}^i \lambda_u$ and $\lambda_j^{(2)} = \sum_{v=j}^k \lambda_v$, $i, j = 1, \ldots, k$. With the further assumption of equal censorship, that is, $G_1 = \cdots = G_k = G$, we obtain the following equations:

$$\sum_{i=1}^k \int \kappa_i^{(p)} \gamma_i d\Lambda = \sum_{i=2}^p \frac{\lambda_i}{\lambda_i^{(1)}} \sum_{u=1}^{i-1} \lambda_u \int w(\gamma_u - \gamma_i) \bar{G} dF + \sum_{j=p}^{k-1} \frac{\lambda_j}{\lambda_j^{(2)}} \sum_{v=j+1}^k \lambda_v \int w(\gamma_v - \gamma_j) \bar{G} dF$$

and

$$\sigma_p^2 = \left\{\sum_{i=2}^p \frac{\lambda_i \lambda_{i-1}^{(1)}}{\lambda_i^{(1)}} + \sum_{j=p}^{k-1} \frac{\lambda_j \lambda_{j+1}^{(2)}}{\lambda_j^{(2)}} + \frac{2\lambda_p \lambda_{p-1}^{(1)} \lambda_{p+1}^{(2)}}{\lambda_p^{(1)} \lambda_p^{(2)}}\right\} \int w^2 \bar{G} dF. \tag{3.2}$$

To evaluate the Pitman efficacy in (3.1), we consider two special umbrella alternatives: Lehmann alternatives, corresponding to the proportional hazards model; and scale alternatives, corresponding to location shifts in log survival times. Note that, under the Lehmann alternative

$$S_{Ni} = S^{1-\theta_i/\sqrt{N}}, \qquad i = 1, \ldots, k,$$

and under the scale alternative

$$S_{Ni} = S(te^{-\theta_i/\sqrt{N}}), \qquad i = 1, \ldots, k,$$

where $\theta_1 \le \cdots \le \theta_p \ge \cdots \ge \theta_k$ for some p, $1 \le p \le k$, with at least one strict inequality. We have $\gamma_i = -\theta_i$ for the Lehmann alternative and $\gamma_i = -\theta_i(1 - \frac{tS'}{S} + \frac{tS''}{S'})$ for the scale alternative for $i = 1, \ldots, k$, where S' and S'' represent the first and second derivatives of the survival function S. Let $\lambda_0 = \lambda_{k+1} = 0$. We observe that

$$\sum_{i=1}^k \int \kappa_i^{(p)} \gamma_i d\Lambda = \left\{\sum_{i=2}^p \frac{\lambda_i}{\lambda_i^{(1)}} \sum_{u=1}^{i-1} \lambda_u (\theta_i - \theta_u) + \sum_{j=p}^{k-1} \frac{\lambda_j}{\lambda_j^{(2)}} \sum_{v=j+1}^k \lambda_v (\theta_j - \theta_v)\right\} \int \varphi \bar{G} dF$$

which, after some algebraic manipulation, can be further simplied as

$$\sum_{i=1}^{k} \int \kappa_i^{(p)} \gamma_i d\Lambda = \Big\{ \sum_{i=1}^{k} C_i^{(p)} \theta_i \Big\} \int \varphi \bar{G} dF.$$

Here

$$C_i^{(p)} = \begin{cases} \lambda_i \{\lambda_{i-1}^{(1)}/\lambda_i^{(1)}\} - \sum_{u=i+1}^{p} \{\lambda_u/\lambda_u^{(1)}\}, & \text{if } 1 \le i \le p-1, \\ \lambda_p \{\lambda_{p-1}^{(1)}/\lambda_p^{(1)} + \lambda_{p+1}^{(2)}/\lambda_p^{(2)}\}, & \text{if } i = p, \\ \lambda_i \{\lambda_{i+1}^{(2)}/\lambda_i^{(2)}\} - \sum_{u=p}^{i-1} \{\lambda_u/\lambda_u^{(2)}\}, & \text{if } p+1 \le i \le k, \end{cases}$$

with $\varphi = w$ for the Lehmann alternative and $\varphi = w(1 - \frac{tS'}{S} + \frac{tS''}{S'})$ for the scale alternative. Hence, the asympototic relative efficiencies of the weighted logrank peak-known umbrella tests are the same as those reported in Liu, Green, Wolf and Crowley (1993) for ordered alternatives. Note that the maximum of $\{\int \varphi \bar{G} dF\}^2 / \int w^2 \bar{G} dF$ occurs at $w(t) = 1$ for the Lehmann alternative, and at $w(t) = \{1 - \frac{tS'(t)}{S(t)} + \frac{tS''(t)}{S'(t)}\}$ for the scale alternative. It demonstrates that the logrank umbrella test is optimal for detecting proportional hazards. Moreover, since the Cauchy-Schwarz inequality implies that $\{\sum_{i=1}^{k} C_i^{(p)} \theta_i\}^2$ attains its maximum when $\theta_i = aC_i^{(p)} + b$ for constants a and b, we have the class of Lehmann and scale alternatives, $\{\theta_i = aC_i^{(p)} + b$ for any constants a and $b\}$, for which the test based on A_P^* has maximum Pitman efficacy.

4. Peak-Unknown Umbrella Tests

As noted in Chen and Wolfe (1990), if the peak of the umbrella is unknown the alternative H_{1U} can be viewed as a union of k individual umbrella alternatives (H_{1U}^p) with the peak p at group $1, \ldots, k$, respectively. This way of viewing H_{1U} leads to a natural extension for the peak-unknown setting to the test procedure which rejects H_0 for large values of

$$A_{\max}^* = \max\{A_1^*, \ldots, A_k^*\},$$

where A_p^*, $p = 1, \ldots, k$, are given by equation (2.11).

Note that, under H_0, for any nonzero constants $a_1, \ldots, a_k$, we have

$$\sum_{p=1}^{k} a_p A_p = \sum_{i=1}^{k} \int \Big\{ \sum_{p=1}^{k} a_p V_i^{(p)} \Big\} dM_i,$$

where the $V_i^{(p)}$ are specified in equation (2.7). Since conditions (2.8) and (2.9) also hold for $\sum_{p=1}^{k} a_p A_p$, where the $V_i^{(p)}$ in (2.8) and (2.9) are now replaced by

$\sum_{p=1}^{k} a_p V_i^{(p)}$, the Martingale Central Limit Theorem and Cramer-Wold device imply that, under H_0, the asymptotic distribution of $(A_1^*, \ldots, A_k^*)$ is a multivariate normal distribution. Moreover, note that

$$\text{Cov}\,(A_p, A_q) = \sum_{i=1}^{k} E \int V_i^{(p)} V_i^{(q)} Y_i (1 - \Delta\Lambda) d\Lambda, \quad p \neq q = 1, \ldots, k.$$

Therefore, we have

$$(A_1^*, \ldots, A_k^*) \xrightarrow{d} N(\mathbf{0}, \mathbf{R}), \quad \text{as } N \to \infty,$$

where $\mathbf{R} = (\sigma_{pq}/\sqrt{\sigma_p^2 \sigma_q^2})$, $\sigma_{pq} = \sum_{i=1}^{k} \int \nu_i^{(pq)} (1 - \Delta\Lambda) d\Lambda$, σ_p^2 is given in (2.9), and $\nu_i^{(pq)}$ is the limit of $V_i^{(p)} V_i^{(q)} Y_i / N$, $p \neq q = 1, \ldots, k$. Consistent estimators for the σ_{pq} are then given by $\hat{\text{Cov}}\,(A_p, A_q)/N$, where

$$\hat{\text{Cov}}\,(A_p, A_q) = \sum_{i=1}^{k} \int V_i^{(p)} V_j^{(q)} Y_i \Big\{1 - \frac{\Delta D - 1}{Y - 1}\Big\} \frac{dD}{Y}, \quad p \neq q = 1, \ldots, k.$$

A consistent estimator for $\mathbf{R}$ is further obtained as

$$\hat{\mathbf{R}} = \Big(\hat{\text{Cov}}\,(A_p, A_q) \Big/ \sqrt{\hat{\text{Var}}\,(A_p) \hat{\text{Var}}\,(A_q)} \Big),$$

where $\hat{\text{Var}}\,(A_p)$ is given by equation (2.10).

Let $(Z_1, \ldots, Z_k)$ be a random vector which has a k-variate normal distribution with zero mean vector and correlation matrix $\hat{\mathbf{R}}$, and let $\text{zmax}(k, \alpha)$ be the upper αth percentile of the distribution of $\max(Z_1, \ldots, Z_k)$. We obtain an approximate level α test for the umbrella alternative H_{1U} by rejecting H_0 if

$$A_{\max}^* \geq \text{zmax}(k, \alpha). \tag{4.1}$$

For any z and $k \leq 7$, the probability $P\{\max(Z_1, \ldots, Z_k) \leq z\}$ can be computed using a program for calculating multivariate normal probabilities (Schervish (1984)). Therefore, the critical value $\text{zmax}(k, \alpha)$ can be found such that $P\{\max(Z_1, \ldots, Z_k) \geq \text{zmax}(k, \alpha)\} = \alpha$.

On the other hand, we find the limit of $V_i^{(p)} V_i(q) Y_i / N$, namely, $\nu_i^{(pq)}$, under the assumption of a common censoring distribution. The σ_{pq} values, for $p < q$, are then obtained in the following:

$$\begin{aligned}
\sigma_{pq} = \Bigg\{ & \sum_{i=1}^{p-1} \lambda_i \Big[\sum_{u=i+1}^{p} \frac{\lambda_u}{\lambda_u^{(1)}} - \frac{\lambda_{i-1}^{(1)}}{\lambda_i^{(1)}} \Big] \Big[\sum_{v=i+1}^{p} \frac{\lambda_v}{\lambda_v^{(1)}} - \frac{\lambda_{i-1}^{(1)}}{\lambda_i^{(1)}} \Big] - \lambda_p \Big[\frac{\lambda_{p-1}^{[1]}}{\lambda_p^{(1)}} + \frac{\lambda_{p+1}^{(2)}}{\lambda_p^{(2)}} \Big] \Big[\sum_{v=p+1}^{q} \frac{\lambda_v}{\lambda_v^{(1)}} - \frac{\lambda_{p-1}^{(1)}}{\lambda_p^{(1)}} \Big] \\
& + \sum_{i=p+1}^{q-1} \lambda_i \Big[\sum_{u=p}^{i-1} \frac{\lambda_u}{\lambda_u^{(2)}} - \frac{\lambda_{i+1}^{(2)}}{\lambda_i^{(2)}} \Big] \Big[\sum_{v=i+1}^{q} \frac{\lambda_v}{\lambda_v^{(1)}} - \frac{\lambda_{i-1}^{(1)}}{\lambda_i^{(1)}} \Big] - \lambda_q \Big[\sum_{u=p}^{q-1} \frac{\lambda_u}{\lambda_u^{(2)}} - \frac{\lambda_{q+1}^{(2)}}{\lambda_q^{(2)}} \Big] \Big[\frac{\lambda_{q-1}^{[1]}}{\lambda_q^{(1)}} + \frac{\lambda_{q+1}^{(2)}}{\lambda_q^{(2)}} \Big] \\
& + \sum_{i=q+1}^{k} \lambda_i \Big[\sum_{u=p}^{i-1} \frac{\lambda_u}{\lambda_u^{(2)}} - \frac{\lambda_{i+1}^{(2)}}{\lambda_i^{(2)}} \Big] \Big[\sum_{v=q}^{i-1} \frac{\lambda_v}{\lambda_v^{(2)}} - \frac{\lambda_{i+1}^{(2)}}{\lambda_i^{(2)}} \Big] \Bigg\} \int w^2 \bar{G} dF.
\end{aligned}$$

For this setting, we compute the $\sigma_{pq}/\sqrt{\sigma_p^2\sigma_q^2}$ values for the case of equal sample sizes, where the values of the σ_p^2 are given in (3.3), and we compute ($k \le 7$) or simulate ($k > 7$) the critical values zmax(k, α) from the k-variate normal distribution with known correlation matrix $\mathbf{R}$. The critical values zmax(k, α), for the case of common censoring distribution, equal sample sizes, $k = 2(1)10$ and $\alpha = .01$, $.05$ and $.10$, are then reported in Table 1. We recommend use of these critical values for situations where the sample sizes are equal and the assumption of common censoring distribution is tenable. Otherwise, we can obtain the estimated correlation matrix $\hat{\mathbf{R}}$ from the data, and compute or simulate the critical value zmax(k, α) from this k-variate normal distribution with (estimated) correlation matrix $\hat{\mathbf{R}}$.

Table 1. Values of zmax(k, a) for common censoring distribution and equal sample sizes.

	k								
α	2	3	4	5	6	7	8	9	10
0.01	2.58	2.66	2.80	2.89	2.89	2.92	2.99	3.01	3.04
0.05	1.96	2.10	2.23	2.28	2.34	2.37	2.38	2.39	2.40
0.10	1.65	1.80	1.92	1.99	2.03	2.07	2.08	2.09	2.10

Suppose that the umbrella alternative H_{1U} is H_{1U}^p for some $p = 1, \ldots, k$. Note that the power of the test based on $A_{\max}^*$ is

$$\begin{aligned} 1 - P\{A_{\max}^* < \text{zmax}(k, \alpha) \mid H_{1U}\} &= 1 - P\{A_i^* < \text{zmax}(k, \alpha),\ i = 1, \ldots, k \mid H_{1U}^p\} \\ &> 1 - P\{A_p^* < \text{zmax}(k, \alpha) \mid H_{1U}^p\}. \end{aligned}$$

Therefore, the test base on $A_{\max}^*$ is consistent under the alternative H_{1U} if each peak-known test based on A_p^* is consistent under the relevant umbrella alternative H_{1U}^p.

Remark 2. When survival in the treatment groups is expected to decrease up to a certain point and then increase with further doses, the appropriate peak-unknown umbrella test would reject the null hypothesis H_0 in favor of the alternative H_{2U} : ($S_1 \ge \cdots \ge S_p \le \cdots \le S_k$, for some p, with at least one strict inequality) for small values of $A_{\min}^* = \min\{A_1^*, \ldots, A_k^*\}$ or for large values of $\max\{-A_1^*, \ldots, -A_k^*\}$. Note that, under H_0, the asymptotic distribution of $(-A_1^*, \ldots, -A_k^*)$ is the same as that of $(A_1^*, \ldots, A_k^*)$. Therefore, for this setting, we suggest rejection of H_0 in favor of H_{2U} if

$$\max\{-A_1^*, \ldots, -A_k^*\} \ge \text{zmax}(k, \alpha). \tag{4.2}$$

5. An Example

Homburger and Treger (1970) studied the carcinogenic effect of transplantation of combined injection sites from previous animal hosts receiving injections of a large dose (500 μg) of a weaker carcinogen, benz[α]-anthracene (BA) in tricaprylin (glycerol trioctanoate), has on tumor growth in the secondary recipients. In particular, they were interested in possible differences in carcinogenic effects relative to the length of time elapsed between the original injections in the host and the site transfers to the transplant recipients.

A group of 40 C57BL/6 J male mice were given subcutaneous injection of 500 μg of BA. Injection-site transfers (from pooling individual sites of these 40 animal) were tranplanted into 10 additional host C57BL/6 J male mice at periods of 8, 12, 16, and 24 weeks after the original injection into the 40 donor mice. In addition, a control group of 50 animals were also injected directly with 500 μg of BA, which was then left *in situ.* The measurement of record for each study group was the time (after the initial transplants or injection, in the case of the control group) at which a tumor was first palpated. For those animals which did not develop tumors, the time recorded is the number of weeks between the initial transplants (or injection for the control group) and the end of the study when animals were sacrificed and autopsied (or death for those which died without tumors). Thus, those animals with no incidence of tumors yield censored data for this study. The Kaplan-Meier (1958) estimates of the survival (tumor free) functions for the five studied groups of animals are presented in Figure 1 and the relevant summary statistics for testing against the umbrella alternative H_{2U} are reported in Table 2.

We observe, from Table 2, that the Peto-Prentice-Wilcoxon peak-unknown umbrella test claims that the survivals have an umbrella pattern with the peak possibly at the third group of injection sites transferred after 12 weeks ($\max\{-A_1^*,\ldots,-A_5^*\} = -A_3^* > \text{zmax}(5, 0.01)$), while the logrank peak-unknown umbrella test concludes that the survivals of the five groups follow an ordered pattern ($\max\{-A_1^*,\ldots,-A_5^*\} = -A_5^* > \text{zmax}(5, 0.01)$). Note that the logrank test is optimal for the proportional hazards model. However, the Kaplan-Meier estimates, in Figure 1, indicate that these five groups may not have proportional hazards. In fact, the Kaplan-Meier estimates suggest an early occurring hazard differences. Therefore, based on the Peto-Prentice-Wilcoxon test, we conclude that, when compared to the tumor times in the control group, there is an accelerated appearance of tumors when the injection sites were transferred into a new host 8 and 12 weeks after the subcutaneous injection of 500 μg of BA, but the accelerated carcinogenesis was less pronounced when the carcinogen was left in the first host for more than 16 weeks. One conjecture for this umbrella pattern, made by Homburger and Treger (1970), is that the immunological defenses of the original host suppressed the growth potential of transformed cells when these remained within the original host, thereby reducing its carcinogenic effect.

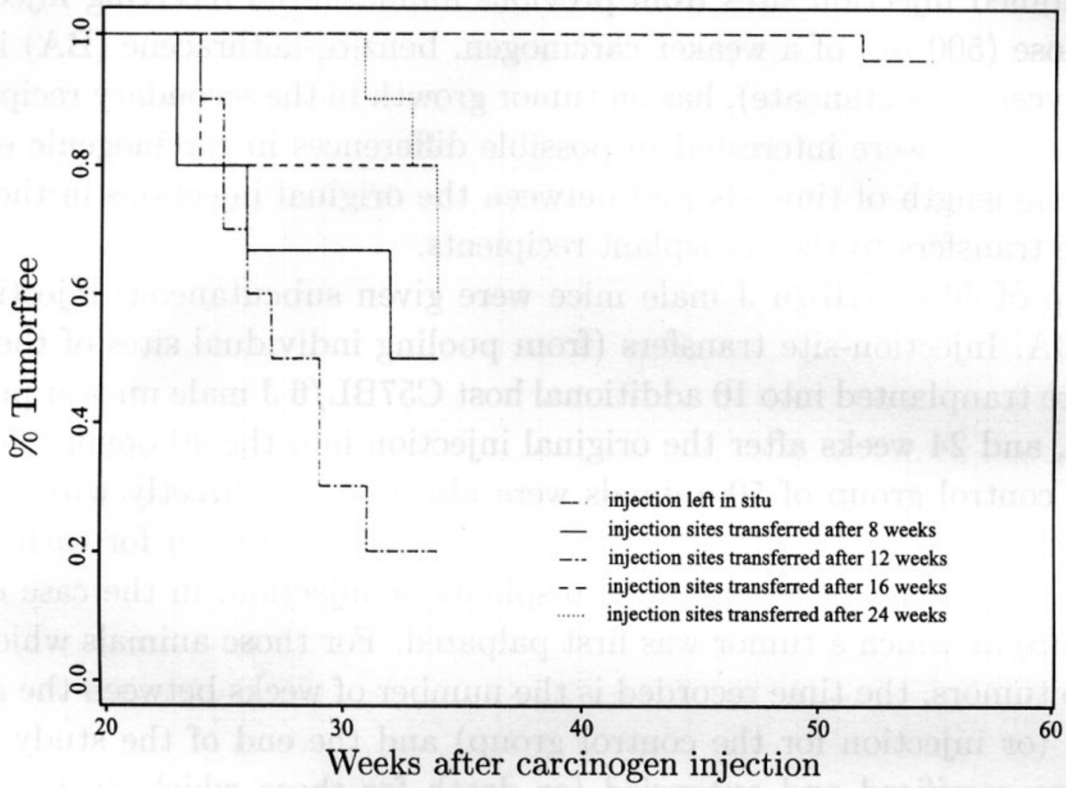

Figure 1. Kaplan-Meier estimates for the injection sites-transfer data.

Table 2. Umbrella test statistics for the injection sites-transfer data.

Peak (p)	1	2	3	4	5
			(a) Logrank		
A_p	6.4897	−8.3364	−14.1065	−9.6509	−12.2950
$\hat{\text{Var}}\,(A_p)$	10.1162	8.1379	6.8822	6.1737	4.9324
A_p^*	2.0404	−2.9223	−5.3772	−3.8841	−5.5360
$\hat{\mathbf{R}}$	1.0000	0.2998	0.1520	−0.1325	−0.7539
		1.0000	0.5836	0.4819	0.0811
			1.0000	0.6812	0.3272
				1.0000	0.6783
	(zmax(5, 0.01) = 2.7937)				1.0000
			(b) Peto-Prentice-Wilcoxon		
A_p	5.8745	−7.4349	−12.4541	−9.1673	−10.9051
$\hat{\text{Var}}\,(A_p)$	6.9137	5.3020	4.8431	4.7738	4.0232
A_p^*	2.2342	−3.2289	−5.6592	−4.1957	−5.4369
$\hat{\mathbf{R}}$	1.0000	0.2848	0.1151	−0.1721	−0.8027
		1.0000	0.6625	0.5486	0.1260
			1.0000	0.7528	0.3836
				1.0000	0.7122
	(zmax(5, 0.01) = 2.8369)				1.0000

6. Monte Carlo Study

To examine the relative level and power performances of the umbrella tests based on A_p^* and $A_{\max}^*$ for umbrella alternatives when observations are subject to random right-censorship and sample sizes are varied from small to moderate, we conducted a Monte Carlo study. We considered $k = 4$ populations with sample sizes $n_1 = \cdots = n_k = n = 10$, 20 and 30 in the level study and with $n = 30$ in the power study.

Exponential and lognormal distributions were considered as survival time distributions and the uniform distribution over $(0, R)$ was used as the censoring distribution. Appropriate uniform, normal and exponential variates were generated by using the IMSL routines RNUN, RNNOR and RNEXP, respectively. Exponential-transformed normal variates then give the necessary lognormal variates. In the level study, the standard exponential distribution and the lognormal distribution with zero normal mean and normal standard deviation $\sigma = 1/2$ were considered. In the power study, we used exponential distributions with various values of the scale parameters (θ_i's) and lognormal distributions with normal standard deviation $\sigma = 1/2$ but different values of the normal means (θ_i's). A variety of R values, corresponding to probabilities of censorship 0.10, 0.30 and 0.50, were considered in the level study. The corresponding uniform distributions for probabilities of censorship 0.10 and 0.30 were then employed as censoring distributions in the power study as well. For example, when survival time distribution is the standard exponential and $p = 0.1$, $R = 9.901$. For the lognormal distribution with zero normal mean and normal standard deviation $\sigma = 1/2$, $R = 3.756$ corresponds to $p = 0.3$. Note that the censoring probabilities were fixed for each population in the level study, while they may be different for the populations involved in the power study due to different survival time distributions.

For each of these settings, we used the critical values in Table 1 and employed 5,000 replications to obtain the level or power estimates under the nominal level $\alpha = 0.05$. Therefore, the maximum standard error for the power estimates is about 0.007 ($\approx \sqrt{(0.5)(0.5)/5000}$). In fact, the standard error for the level estimates is less than 0.003 ($\approx \sqrt{(0.05)(0.95)/5000}$). The level estimates are presented in Table 3 and the power estimates are reported in Tables 4 and 5. Note that the results in Table 5 provide information about how the peak-"known" umbrella test performs when it corresponds to the wrong peak.

It is evident, upon examination of Table 3, that the logrank and Peto-Prentice-Wilcoxon umbrella tests hold their levels reasonably well when the common sample size is at least 20 and the degree of censoring is light (the corresponding probability of censorship is 0.1) or moderate (the associated probability of censorship is 0.3). The power study reported in Table 4 shows that the logrank test is superior to the Peto-Prentice-Wilcoxon test for Lehmann alternatives, while the Peto-Prentice-Wilcoxon test is more efficient than the logrank test for scale alternatives. This is not surprising since exponential distributions preserve the proportional hazards, but the hazards are far from being proportional for lognormal distributions. The results for the peak-known umbrella tests, in particular, coincide with those obtained from comparing their asymptotic relative efficiencies, as presented in Liu, Green, Wolf and Crowley (1993).

Table 3. Level estimates for nominal level $\alpha = 0.05$, uniform censoring and $n_1 = \cdots = n_4 = n$.

	Censoring	Peak-known			Peak-unknown		
n	probability	LR	P-P-W	G-W	LR	P-P-W	G-W
		(a) Exponential					
10	0.1	0.046	0.045	0.044	0.045	0.040-	0.041-
	0.3	0.043-	0.042-	0.043-	0.042-	0.036-	0.035-
	0.5	0.044	0.043-	0.041-	0.041-	0.035-	0.035-
20	0.1	0.045	0.045	0.045	0.046	0.044	0.044
	0.3	0.044	0.044	0.046	0.045	0.044	0.045
	0.5	0.047	0.047	0.045	0.042-	0.040-	0.040-
30	0.1	0.052	0.049	0.049	0.048	0.046	0.045
	0.3	0.048	0.049	0.051	0.045	0.046	0.045
	0.5	0.048	0.050	0.048	0.044	0.045	0.045
		(b) Lognormal					
10	0.1	0.046	0.044	0.046	0.044	0.035-	0.037-
	0.3	0.044	0.043-	0.044	0.047	0.037-	0.037-
	0.5	0.043-	0.042-	0.043-	0.045	0.039-	0.036-
20	0.1	0.044	0.045	0.045	0.046	0.045	0.044
	0.3	0.047	0.046	0.045	0.045	0.043-	0.045
	0.5	0.048	0.049	0.048	0.042-	0.041-	0.040-
30	0.1	0.052	0.049	0.049	0.048	0.046	0.045
	0.3	0.048	0.049	0.051	0.048	0.044	0.045
	0.5	0.051	0.050	0.048	0.046	0.047	0.046

Exponential: $f(t) = \exp(-t)$
Lognormal: $f(t) = \sqrt{2}/(t\sqrt{\pi})\} \exp\{-2(\log t)^2\}$

Table 4. Power estimates for $k = 4$, nominal level $\alpha = 0.05$, uniform censoring distribution $U(0, R)$, and $n_1 = \cdots = n_4 = 30$.

Parameters					Ordered test		Peak-known		Peak-unknown	
θ_1	θ_2	θ_3	θ_4	R	LR	P-P-W	LR	P-P-W	LR	P-P-W
					(a) Exponential					
1	1	1.5	2	9.901	0.790	0.697	0.790	0.697	0.588	0.479
				3.185	0.663	0.609	0.663	0.609	0.421	0.370
1	1.5	1.5	2	9.901	0.738	0.661	0.738	0.661	0.503	0.429
				3.185	0.620	0.586	0.620	0.586	0.398	0.364
1	1.5	2	1	9.901	0.200	0.184	0.876	0.805	0.768	0.663
				3.185	0.168	0.160	0.764	0.709	0.615	0.555
1	1.5	2	1.5	9.901	0.606	0.564	0.697	0.616	0.613	0.522
				3.185	0.512	0.473	0.581	0.523	0.477	0.435
1.5	2	1.5	1	9.901	0.001	0.001	0.683	0.605	0.598	0.508
				3.185	0.002	0.005	0.570	0.515	0.465	0.420
1.5	2	1	1	9.901	0.000	0.000	0.640	0.527	0.570	0.475
				3.185	0.001	0.001	0.488	0.433	0.429	0.380
2	1.5	1.5	1	9.901	0.000	0.000	0.739	0.672	0.529	0.451
				3.185	0.000	0.001	0.620	0.577	0.395	0.363
2	1.5	1	1	9.901	0.000	0.000	0.791	0.697	0.583	0.457
				3.185	0.000	0.000	0.647	0.546	0.405	0.360
					(b) Lognormal					
0	0	0.2	0.4	11.219	0.838	0.874	0.838	0.874	0.655	0.698
				3.576	0.766	0.800	0.766	0.800	0.563	0.604
0	0.2	0.2	0.4	11.219	0.799	0.849	0.799	0.849	0.611	0.680
				3.576	0.721	0.774	0.721	0.774	0.517	0.576
0	0.2	0.4	0	11.219	0.243	0.262	0.931	0.946	0.839	0.873
				3.576	0.225	0.243	0.891	0.915	0.766	0.803
0	0.2	0.4	0.2	11.219	0.634	0.706	0.799	0.835	0.710	0.761
				3.576	0.568	0.625	0.739	0.769	0.625	0.674
0.2	0.4	0.2	0	11.219	0.002	0.003	0.807	0.843	0.702	0.750
				3.576	0.003	0.002	0.736	0.771	0.618	0.654
0.2	0.4	0	0	11.219	0.000	0.000	0.753	0.766	0.653	0.682
				3.576	0.001	0.001	0.663	0.679	0.552	0.591
0.4	0.2	0.2	0	11.219	0.000	0.000	0.793	0.846	0.597	0.676
				3.576	0.000	0.000	0.730	0.787	0.516	0.577
0.4	0.2	0	0	11.219	0.000	0.000	0.831	0.871	0.646	0.693
				3.576	0.000	0.000	0.771	0.805	0.564	0.607

Exponential: $f_i(t) = (1/\theta_i) \exp\{-t/\theta_i\}$

Lognormal: $f_i(t) = \{\sqrt{2}/(t\sqrt{\pi})\} \exp\{-2(\log t - \theta_i)^2)\}$

Table 5. Power estimates for $k = 4$, nominal level $\alpha = 0.05$, uniform censoring distribution $U(0, R)$, and $n_1 = \cdots = n_4 = 30$.

Parameters					A_2^*		A_3^*		$A_{\max}^*$	
θ_1	θ_2	θ_3	θ_4	R	LR	P-P-W	LR	P-P-W	LR	P-P-W
(a) Exponential										
1	1	2	1.5	9.901	0.008	0.009	0.642	0.554	0.563	0.456
				3.185	0.011	0.010	0.477	0.424	0.421	0.370
1	1.5	2	1.5	9.901	0.199	0.182	0.697	0.616	0.613	0.522
				3.185	0.180	0.165	0.581	0.523	0.477	0.435
1	1.5	2	1	9.901	0.559	0.518	0.876	0.805	0.768	0.663
				3.185	0.490	0.454	0.764	0.709	0.615	0.555
(b) Lognormal										
0	0	0.4	0.2	11.219	0.010	0.011	0.739	0.757	0.661	0.693
				3.756	0.011	0.011	0.657	0.680	0.575	0.602
0	0.2	0.4	0.2	11.219	0.200	0.219	0.799	0.835	0.710	0.761
				3.756	0.191	0.210	0.739	0.769	0.625	0.674
0	0.2	0.4	0	11.219	0.548	0.635	0.931	0.946	0.839	0.873
				3.756	0.514	0.567	0.891	0.915	0.766	0.803

Exponential: $f_i(t) = (1/\theta_i)\exp\{-t/\theta_i\}$
Lognormal: $f_i(t) = \{\sqrt{2}/(t\sqrt{\pi})\}\exp\{-2(\log t - \theta_i)^2\}$

We observe from the simulation results that the test based on A_p^* has excellent power against umbrella pattern treatment effects when the peak is correctly chosen. However, we also see, from Table 4 , that the power of the ordered test based on A_k^* drops sharply when there is a downturn in the umbrella. Similarly we observe, from Table 5, that the power of the peak-known umbrella test declines when the peak is incorrectly selected. In these cases, the peak-unknown test based on $A_{\max}^*$ is more powerful than the peak-known umbrella test with incorrect peak. Note that, across all situations considered in the power study, the test based on $A_{\max}^*$ has at least 50 percent (60 percent, in the case of $n = 30$) of the power of the test based on A_p^*.

7. Conclusion

Testing procedures based on weighted logrank statistics are considered for testing against umbrella alternatives when the peak of the umbrella is known or unknown. The test based on $A_{\max}^*$ also provides a reasonable estimation of the location of the peak group in those problems involving peak-unknown umbrella pattern treatment effects, since if the null hypothesis is rejected and $A_{\max}^* = A_{\hat{p}}^*$, then we may estimate the unknown peak group to be at $\hat{p}$. The question of how accurate is the point estimation and a possible interval estimation of the unknown peak group will then deserve a future study. Simpson and Margolin (1986) point out that dose-response relationships may be subject to downturns at high doses so test procedures with partial information about the umbrella peak are of interest in dose-response studies. This issue will be addressed in a separate article.

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