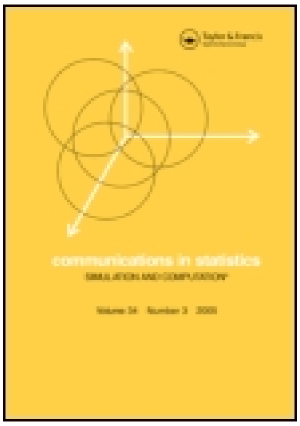

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Nonparametric Multiple Test Procedures for Dose Finding

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ABSTRACT

We consider identifying the minimum effective dose (MED) in a one-way layout, where the MED is defined to be the lowest dose level that is more effective than the zero-dose control. Proposed herein are two rank-based nonparametric step-down closed testing procedures that do not make order assumptions on the dose-response relationship. The corresponding p-value for the estimated MED is computed. A numerical example is given to illustrate the proposed tests. Finally, the results of a Monte Carlo study of the relative error rate and power performances are reported.

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Mathematics Subject Classification: 62G10; 62K10.

1. INTRODUCTION

To investigate the effect of a compound in a drug development study, a dose–response experiment is often conducted in a one-way layout in which several increasing dose levels of the compound, including a zero-dose to serve as a control, are administered to separate groups of subjects. One major concern in this case is to identify the lowest dose level with a mean exceeds that of the zero-dose control, which is commonly referred as the minimum effective dose (MED, see Ruberg, 1989).

When the responses are assumed to be normally distributed, Williams (1971, 1972) proposed one of the first dose-finding procedures. His test is a step-down closed testing procedure based on the isotonic regression of the sample means for a monotonic dose-response relationship. Ruberg (1989) considered single-step multiple testing procedures based on different contrasts of sample means for identifying the MED. Tamhane et al. (1996) further investigated some stepwise closed testing procedures based on a variety of contrasts of sample means for the dose-finding problem. Finally, they suggested using pairwise and Helmert contrasts incorporated into the proposed step-down testing scheme.

When the normal assumption is not tenable, many nonparametric procedures have been proposed for this MED identification problem. Shirley (1977) considered multiple test based on the isotonic regression of the Kruskal–Wallis rank averages (Kruskal and Wallis, 1952) for a monotonic dose–response relationship. Her procedure is a nonparametric analogue of Williams' test (Williams, 1971,1972). Williams (1986) further provided a modification of Shirley's test (Shirley, 1977). Chen and Wolfe (1993) suggested multiple testing procedures based on the rank-based isotonic regression estimators for umbrella pattern of dose–response relationship. Chen (1999) further proposed a step-down closed testing procedure based on the two-sample Mann–Whitney statistic (Mann and Whitney, 1947) for identifying the MED. Note that the procedures based on contrasts are more convenient to compute than those based on isotonic regressions; moreover, it is known that in some settings step-down procedures are more powerful than either their step-up or single-step counterparts for simultaneous testing problems. Therefore, in this paper we introduce the nonparametric procedures based on two different contrasts of the Kruskal–Wallis rank averages incorporated with the step-down closed testing scheme. We then compute the associated p-value of the identified MED, which is defined to be the smallest level of significance at which the dose level would be declared as the MED.

Section 2 proposes two rank-based nonparametric step-down closed testing procedures for identifying the MED. It is seen that one of the proposed rank-based procedure is identical to Chen's test (Chen, 1999) based on Mann–Whitney count statistic. Section 3 gives a numerical example to illustrate the tests. Section 4 presents the results of a Monte Carlo simulation study of the relative error rate and power performances of the competing tests. Finally, Sec. 5 contains some conclusions.

2. THE PROPOSED PROCEDURES

Denote a set of increasing dose levels by $0, 1, \ldots, k$, where 0 corresponds to the zero-dose level (or placebo control). Consider a one-way layout setting and let X_{ij} denote the jth observation on the ith dose level, $i = 0, 1, \ldots, k,\ j = 1, \ldots, n_i$. We assume that all observations X_{ij} are mutually independent, each with a continuous distribution function $F_i,\ i = 0, 1, \ldots, k,\ j = 1, \ldots, n_i$. Henceforward, for the sake of convenience, we restrict to the case of equal sample size, that is, $n_0 = n_1 = \cdots = n_k = n$; the numerical example and the simulation study are confined to this case. In the final section, we discuss how to extend the procedures to the case of unequal sample size. In this paper, we wish to identify the MED, which is defined as $\text{MED} = \min\{i : F_i < F_0\}$, i.e., the smallest i such that the response in the ith population is stochastically larger than that in the control. This problem is often formulated as a sequence of hypotheses testing problems as follows:

$$\begin{aligned} &H_{0i} : F_0 = F_1 = \cdots = F_{i-1} = F_i \quad \text{vs.} \\ &H_{1i} : F_0 = F_1 = \cdots = F_{i-1} > F_i, \quad i = 1, \ldots, k. \end{aligned} \tag{2.1}$$

If i^* is the smallest i for which H_{0i} is rejected, then the i^*th dose is identified to be the MED, that is, $\widehat{\text{MED}} = i^*$.

As noted in Tamhane et al. (1996), the family of hypotheses $H = \{H_{0i} : 1 \le i \le k\}$ is closed under intersection in the sense that $H_{0i} \in H$ and $H_{0i'} \in H$ imply that $H_{0i} \cap H_{0i'} \in H$. Hence, a α-level closed procedure that includes separate α-level tests of individual H_{0i}, applied in a step-down manner can be employed in finding the MED. Moreover, the closed testing scheme strongly controls the familywise error rate (FWE), which is defined as $\text{FWE} = P\{\text{at least one true } H_{0i} \text{ is rejected}\}$. Therefore, we consider using two sets of contrasts of Kruskal–Wallis rank averages incorporated into the step-down testing scheme for identifying the MED.

When the dose levels $0 \sim i$ are under study, let $R_{sj}^{(i)}$ be the Kruskal–Wallis rank of X_{sj} in the combined $i+1$ samples, and let $R_s^{(i)} = \sum_{j=1}^{n} R_{sj}^{(i)}$ denote the sum of ranks of the sth dose level, $i = 1, \ldots, k$, $s = 0, 1, \ldots, i$, and $j = 1, \ldots, n$. Contrasts based on $R_s^{(i)}, s = 0, 1, \ldots, i$, can be used for testing H_{0i} against H_{1i} of (2.1). We consider the following two types of contrasts:

(I) Pairwise Contrasts. The pairwise-type statistic comparing the ith dose level with the control is defined by $P_i = R_i^{(i)} - R_0^{(i)},\ i = 1, \ldots, k$. Let

$$JP_i = P_i \Big/ \sqrt{Var(P_i)}, \quad i = 1, \ldots, k, \tag{2.2}$$

where $Var(P_i) = nN_i(N_i + 1)/6$, with $N_i = (i+1)n$, is the null (H_{0i}) variance of P_i. Note that, if there are ties among the N_i observations, then $Var(P_i)$ is modified by replacing the term $N_i + 1$ with $N_i + 1 - \sum_{j=1}^{g} t_j(t_j^2 - 1)/[N_i(N_i - 1)]$, where g is the number of tied groups and t_j is the size of the tied group j. Moreover, due to the facts that JP_i has limiting standard normal distribution under H_{0i} and the correlation between JP_i and $JP_{i'}$ approaches $1/2$, the results of Theorem A13 of Hettmansperger (1984) imply that, under the complete null hypothesis $H_{0k}, (JP_1, \ldots, JP_k)$ has asymptotic multivariate normal distribution with zero mean vector and correlation matrix $\mathbf{R}$, where

$$\mathbf{R} = \begin{bmatrix} 1 & & 1/2 \\ & \ddots & \\ 1/2 & & 1 \end{bmatrix}.$$

(II) Helmert Contrasts. The Helmert-type statistic comparing the ith dose level with the combined all lower dose levels (including the control) is defined by $H_i = iR_i^{(i)} - (R_0^{(i)} + \cdots + R_{i-1}^{(i)}), i = 1, \ldots, k$. Define

$$JH_i = H_i \Big/ \sqrt{Var(H_i)}, \quad i = 1, \ldots, k, \tag{2.3}$$

where $Var(H_i) = iN_i^2(N_i + 1)/12$ is the null (H_{0i}) variance of H_i. The modification of $Var(H_i)$ for ties is the same as in (I). It can be shown that the test based on JH_i is identical to Chen's test (Chen, 1999), a Helmert-type Mann–Whitney statistic. Therefore, the asymptotic null (H_{0k}) distribution of $(JH_1, \ldots, JH_k)$ is multivariate normal with zero mean vector and identity correlation matrix.

We now describe how to incorporate the proposed procedures JP_i or JH_i into the step-down closed testing scheme suggested by Tamhane et al. (1996). First, we let $(Z_1, \ldots, Z_k)$ be asymptotic multivariate normal with zero mean vector and common correlation ρ. (Here Z_i refers to JP_i and JH_i when $\rho = 1/2$ and 0, respectively.) Let $Z^{\alpha}_{i,\rho}$ denote the upper αth percentile of the distribution of $Z_{(i)} = \max(Z_1, \ldots, Z_i)$, $i = 1, \ldots, k$. To identify the MED at level α, we first let $k_1 = k$ and find $Z_{(k_1)} = \max(Z_1, \ldots, Z_{k_1})$. Define $d(k_1)$ to be the antirank of $Z_{(k_1)}$, i.e., $Z_{(k_1)} = Z_{d(k_1)}$. Then, if $Z_{(k_1)} > Z^{\alpha}_{k_1,\rho}$, we reject H_{0i} for $i = d(k_1), \ldots, k_1$, and go to the second step with $k_2 = d(k_1) - 1$; otherwise, stop testing and accept all the null hypotheses. In general, at the jth step, let $k_j = d(k_{j-1}) - 1$. If $Z_{(k_j)}$ or $Z_{d(k_j)} > Z^{\alpha}_{k_j,\rho}$, then reject H_{0i} for $i = d(k_j), \ldots, k_j$; otherwise, stop testing. When the testing stops at, say, the mth step, then identify the MED as $d(k_{m-1})$ or $k_m + 1$.

Next we show how to obtain the p-value of the identified MED, which is the smallest significance level at which the dose level would be declared as the MED (Wright, 1992). In general, at the jth step for testing H_{0k_j}, let $z_{(k_j)}$ be the observed value of $Z_{(k_j)}$, first compute the null (H_{0k_j}) probability

$$\begin{aligned} p'(k_j) &= P\{Z_{(k_j)} \geq z_{(k_j)}\} \\ &= P\{\text{at least one } Z_t \geq z_{(k_j)}, t = 1, \ldots, k_j\}, \quad j = 1, 2, \ldots \end{aligned}$$

Note that $p'(k_j)$ can be computed by using the PROBMC function of SAS for $\rho = 0.5$, or by $1 - [\Phi(z_{(k_j)})]^{k_j}$ for $\rho = 0$, where $\Phi(\cdot)$ is the distribution function of a standard normal variable. The adjusted p-value is then defined to be

$$p(k_j) = \max\{p'(k_j), p'(k_{j-1}), \ldots, p'(k_1)\}, \quad j = 1, 2, \ldots \tag{2.4}$$

Then, the MED can be identified at the significance level α based on the adjusted p-vlaues. That is, at the jth step, if $p(k_j) < \alpha$, then reject H_{0i} for $i = d(k_j), \ldots, k_j$. If the testing stops at, say, the mth step, then the identified MED is $k_m + 1$ and the p-value of this conclusion is $p(k_{m-1})$, which provides a measure of the strength of evidence for the rejection of $H_{0k_{m-1}}: F_0 = F_1 = \cdots = F_{k_{m-1}}$.

3. EXAMPLE

We consider the data set in Table 1, which corresponds to the third replication of the Ames test (Ames et al., 1975) as reported in Simpson

Table 1. Revertant colonies for acid red 114, TA98, hamster liver activation.

Dose (μg/mL)					
0	100	333	1000	3333	10000
23	27	28	41	28	16
22	23	37	37	21	19
14	21	35	43	30	13

and Margolin (1986). These data, also analyzed in Chen and Wolfe (1993) and Chen (1999), contain five dose levels and a zero-dose control. There are three observations in each dose level. The observations represent the numbers of visible revertant colonies observed on plates containing Salmonella bacteria of strain TA98 and exposed to different doses of Acid Red 114.

The values of the contrasts, along with their corresponding tie-adjusted variances, and the statistics computed by using formulas (2.2) and (2.3) are shown in Table 2. Table 2 also contains the critical values $Z_{i,\rho}^{0.05}$, which are taken from Hochberg and Tamhane (1987). We wish to identify the MED at $\alpha = 0.05$ level.

(I) Procedure *JP*. At the first step, $k_1 = 5$ and $z_{(5)} = z_3 = 2.727$ (with adjusted p-value $= p(5) = p'(5) \approx 0.0138$). Since $z_{(5)} > Z_{5,\rho=0.5}^{0.05} = 2.23$ (or $p(5) < 0.05$), we go to the second step with $k_2 = 3 - 1 = 2$. Note that $z_{(2)} = z_2 = 2.320$ (with $p'(2) \approx 0.0190$ and hence $p(2) \approx \max\ \{0.0138, 0.0190\} = 0.0190$) and $z_{(2)} > Z_{2,\rho=0.5}^{0.05} = 1.92$ (or $p(2) < 0.05$), so we go to the third step with $k_3 = 3 - 2 = 1$. Now $z_{(1)} = z_1 = 0.886$ (with $p'(1) = 0.1867$ and so $p(1) \approx \max\{0.0138, 0.0190, 0.1867\} = 0.1867$), since $z_{(1)} < Z^{0.05} = 1.645$ (or $p(1) > 0.05$) and hence we stop testing.

Table 2. Calculation of the proposed statistics and critical values.

	Pairwise				Helmert			
i	P_i	$Var(P_i)$	JP_i	$Z_{i,\rho=0.5}^{0.05}$	H_i	$Var(H_i)$	JH_i	$Z_{i,\rho=0}^{0.05}$
1	4.0	20.40	0.886	1.645	4	20.40	0.886	1.645
2	15.5	44.63	2.320	1.92	27	133.88	2.334	1.95
3	24.0	77.45	2.727	1.06	52	464.73	2.412	2.12
4	10.5	119.14	0.962	2.16	−15	1191.43	−0.435	2.23
5	−9.5	170.29	−0.728	2.23	−123	2554.41	−2.434	2.32

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Table 3. Testing results of the procedures.

Procedure	Step (j)	k_j	$Z_{(k_j)}$	$d(k_j)$	$Z^{0.05}_{k_j,\rho}$	$p'(k_j)$	$p(k_j)$
JP	1	5	2.727	3	2.23	0.0138	0.0138
	2	2	2.320	2	1.92	0.0190	0.0190
	3	1	0.886	1	1.645	0.1867	0.1867
JH	1	5	2.412	3	2.32	0.0394	0.0394
	2	2	2.334	2	1.95	0.0197	0.0394
	3	1	0.886	1	1.645	0.1867	0.1867

Therefore, we estimate that the MED is the second dose level at $\alpha = 0.05$, where the corresponding p-value of this conclusion is $p(2) \approx 0.0190$.

(II) Procedure *JH*. At the first step, $k_1 = 5$ and $z_{(5)} = z_3 = 2.412$ (with adjusted p-value $= p(5) = p'(5) \approx 0.0394$). Since $z_{(5)} > Z^{0.05}_{5,\rho=0.5} = 2.32$ (or $p(5) < 0.05$), we go to the second step with $k_2 = 3 - 1 = 2$. Note that $z_{(2)} = z_2 = 2.334$ (with $p'(2) \approx 0.0197$ and hence $p(2) \approx \max\{0.0394, 0.0197\} = 0.0394$) and $z_{(2)} > Z^{0.05}_{2,\rho=0.5} = 1.95$ (or $p(2) < 0.05$), so we go to the third step with $k_3 = 2 - 1 = 1$. Now $z_{(1)} = z_1 = 0.886$ (with $p'(1) = 0.1867$ and so $p(1) \approx \max\{0.0394, 0.0197, 0.1867\} = 0.1867$), since $z_{(1)} < Z^{0.05} = 1.645$ (or $p(1) > 0.05$) and hence we stop testing. Thus, MED is also estimated with the second dose level at $\alpha = 0.05$, where the corresponding p-value of this conclusion is $p(2) \approx 0.0394$. These results for the proposed *JP* and *JH* tests are summarized in Table 3.

For these data, at the $\alpha = 0.05$ level, both the proposed procedures *JP* and *JH* estimate the second dose level as the MED, which agree with the finding of Chen's test (Chen, 1999); however, Chen and Wolfe's test (Chen and Wolfe, 1993) with an estimation of the umbrella peak fails to identify the second dose level. In fact, they conclude that the third dose level is the only one that is more effective than the zero-dose control.

4. SIMULATION STUDY

We conducted a Monte Carlo study to compare the relative level and power performances of the proposed procedures *JP* and *JH* with the parametric analogues *TP* and *TH* suggested by Tamhane et al. (1996). In the study, the number of dose levels k considered, excluding control, was 4 and 5. The common sample size n was assumed to be 5 in each

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dose level. Using $\alpha = 0.05$, the critical constants for *TP* and *TH* were also taken from Hochberg and Tamhane (1987).

Some alternative configurations, both monotone, including step and linear responses, and nonmonotone (umbrella pattern) cases were considered. The complete null configuration was also included in the simulation study. In this case, none of the doses are effective compared to control, so that the true MED is defined to be $k + 1$. In each of these settings, the independent random variables with distributions $N(\mu_i, 5)$, Cauchy$(\mu_i, 1)$, and Exp(μ_i) were generated using the RANNOR, RANCAU, and RANEXP functions in SAS, respectively. Here μ_0 is zero for normal and Cauchy models, and one for exponential model. The study was replicated 10,000 times for each of the configurations. Tables 4 and 5 present the estimates of the FWE and power of the four tests for $k = 4$ and 5, respectively. For the complete null configuration, the estimates of the power are not listed in the tables since the main purpose of including this case in the study is to verify control of the error rate for small sample sizes. For configurations with true MED $= 1$ in which no type I error is involved, the entry of estimated FWE $= 0.0000$ is omitted for all procedures. The respective average powers for true MED $= 1$, true MED > 1, and for all cases are also included in the tables.

First, the estimates of the FWE reveal that the proposed procedures *JP* and *JH* have excellent control of the FWE under all configurations (Since they are all less than $0.05 + 1.96[(0.05)(0.95)/10000]^{1/2} = 0.0543$); while the existing procedures *TP* and *TH* fail to do so for exponential model, in which they are too liberal under the complete null hypothesis, and, on the other hand, too conservative under the partial null configurations.

Next, from the estimates of the power, we observe the general result that the pairwise-type tests are better than the Helmert-type tests when true MED $= 1$, otherwise the result is reversed. Moreover, as expected, the parametric procedures *TP* and *TH* outperform the proposed nonparametric procedures *JP* and *JH* in the normal model. However, these new tests *JP* and *JH* are found to be quite competitive for true MED $= 1$ and MED > 1, respectively. Furthermore, they both perform uniformly better for heavy-tailed Cauchy distribution. They remain to be the best tests in the exponential model when true MED are lower doses, e.g., true MED $= 1$ or 2. It may seem that their performances in power degrade somehow for higher doses of true MED. For example, tests *TH* and *JH* have better power for true MED $= k - 1$, while *TH* and *TP* become the best tests when true MED $= k$. However, it should be noted that the parametric procedures *TP* and *TH* fail to control the FWE strongly in the case of exponential model.

Table 4. Estimated FWE and power for $\alpha = 0.05$, $k = 4$, and $n = 5$.

				True	FWE				Power			
μ_1	μ_2	μ_3	μ_4	MED	*TP*	*TH*	*JP*	*JH*	*TP*	*TH*	*JP*	*JH*
Normal Distribution												
0	0	0	0	5	0.0536	0.0508	0.0456	0.0355				
0	0	0	5	4	0.0496	0.0530	0.0426	0.0455	0.8305	0.9218	0.6063	0.9089
0	0	5	5	3	0.0501	0.0514	0.0470	0.0534	0.8448	0.9224	0.6482	0.8941
0	5	5	5	2	0.0505	0.0500	0.0488	0.0467	0.8671	0.9138	0.7136	0.8640
5	5	5	5	1	—	—	—	—	0.9471	0.8982	0.8854	0.6836
4	4	4	4	1	—	—	—	—	0.8101	0.7164	0.7112	0.4831
0	0	4	5	3	0.0498	0.0498	0.0493	0.0519	0.6804	0.8288	0.4964	0.7676
0	3	4	5	2	0.0488	0.0409	0.0452	0.0345	0.4785	0.5707	0.3668	0.4970
2	3	4	5	1	—	—	—	—	0.3484	0.2738	0.2927	0.1822
0	4	5	4	2	0.0444	0.0412	0.0425	0.0375	0.7255	0.8149	0.5726	0.7343
0	4	5	3	2	0.0516	0.0483	0.0466	0.0401	0.7170	0.8059	0.5577	0.7261
0	4	5	2	2	0.0439	0.0418	0.0434	0.0380	0.7251	0.8135	0.5592	0.7260
3	4	5	4	1	—	—	—	—	0.6211	0.5280	0.5364	0.3553
3	4	5	3	1	—	—	—	—	0.6261	0.5352	0.5376	0.3503
3	5	4	3	1	—	—	—	—	0.6351	0.5674	0.5514	0.3843
3	5	4	2	1	—	—	—	—	0.6390	0.5711	0.5573	0.3830
3	5	3	2	1	—	—	—	—	0.6425	0.5723	0.5510	0.3774
Average power for true MED = 1									0.6587	0.5828	0.5779	0.3999
Average power for true MED > 1									0.7336	0.8240	0.5651	0.7648
Average power for all cases									0.6961	0.7034	0.5715	0.5823

(continued)

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Table 4. Continued.

					FWE				Power			
μ_1	μ_2	μ_3	μ_4	True MED	*TP*	*TH*	*JP*	*JH*	*TP*	*TH*	*JP*	*JH*
Cauchy Distribution												
0	0	0	0	5	0.0348	0.0358	0.0444	0.0397				
0	0	0	5	4	0.0285	0.0281	0.0437	0.0390	0.2960	0.3690	0.4351	0.6926
0	0	5	5	3	0.0332	0.0260	0.0446	0.0443	0.2907	0.3604	0.4536	0.6587
0	5	5	5	2	0.0321	0.0239	0.0466	0.0373	0.3019	0.3369	0.4888	0.6010
5	5	5	5	1	—	—	—	—	0.3582	0.3049	0.5830	0.4950
4	4	4	4	1	—	—	—	—	0.2821	0.2319	0.5078	0.4097
0	0	4	5	3	0.0307	0.0234	0.0447	0.0416	0.2232	0.2808	0.3932	0.5778
0	3	4	5	2	0.0259	0.0166	0.0458	0.0325	0.1615	0.1818	0.3382	0.4307
2	3	4	5	1	—	—	—	—	0.1250	0.0896	0.3073	0.2391
0	4	5	4	2	0.0328	0.0220	0.0449	0.0352	0.2347	0.2689	0.4253	0.5365
0	4	5	3	2	0.0288	0.0189	0.0412	0.0324	0.2310	0.2659	0.4215	0.5461
0	4	5	2	2	0.0326	0.0204	0.0479	0.0370	0.2326	0.2669	0.4196	0.5368
3	4	5	4	1	—	—	—	—	0.2150	0.1698	0.4376	0.3514
3	4	5	3	1	—	—	—	—	0.2157	0.1662	0.4425	0.3553
3	5	4	3	1	—	—	—	—	0.2212	0.1745	0.4520	0.3670
3	5	4	2	1	—	—	—	—	0.2219	0.1779	0.4510	0.3690
3	5	3	2	1	—	—	—	—	0.2117	0.1692	0.4392	0.3584
Average power for true MED = 1									0.2314	0.1855	0.4526	0.3681
Average power for true MED > 1									0.2465	0.2913	0.4219	0.5725
Average power for all cases									0.2389	0.2384	0.4372	0.4703

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Exponential Distribution												
1	1	1	1	5	0.0579	0.0723	0.0452	0.0363				
1	1	1	6	4	0.0023	0.0036	0.0440	0.0409	0.7629	0.8790	0.3722	0.6183
1	1	6	6	3	0.0002	0.0002	0.0468	0.0446	0.4673	0.5994	0.3864	0.5769
1	6	6	6	2	0.0002	0.0000	0.0421	0.0302	0.3121	0.3895	0.4207	0.5365
6	6	6	6	1	—	—	—	—	0.2350	0.1694	0.5607	0.3536
5	5	5	5	1	—	—	—	—	0.1983	0.1436	0.4770	0.2919
1	1	5	6	3	0.0002	0.0002	0.0455	0.0416	0.3765	0.4990	0.3366	0.5053
1	4	5	6	2	0.0000	0.0000	0.0423	0.0270	0.1398	0.1850	0.2867	0.3714
3	4	5	6	1	—	—	—	—	0.0377	0.0222	0.2840	0.1578
1	5	6	5	2	0.0000	0.0000	0.0412	0.0290	0.2523	0.3138	0.3553	0.4630
1	5	6	4	2	0.0000	0.0000	0.0402	0.0272	0.2814	0.3470	0.3529	0.4546
1	5	6	3	2	0.0002	0.0002	0.0419	0.0277	0.3264	0.3941	0.3536	0.4548
4	5	6	5	1	—	—	—	—	0.0985	0.0624	0.4075	0.2317
4	5	6	4	1	—	—	—	—	0.1103	0.0680	0.3942	0.2263
4	6	5	4	1	—	—	—	—	0.1257	0.0786	0.4138	0.2380
4	6	5	3	1	—	—	—	—	0.1515	0.0960	0.4036	0.2301
4	6	4	3	1	—	—	—	—	0.1717	0.1155	0.4029	0.2305
Average power for true MED = 1									0.1411	0.0945	0.4180	0.2450
Average power for true MED > 1									0.3648	0.4509	0.3581	0.4976
Average power for all cases									0.2530	0.2727	0.3880	0.3713

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Table 5. Estimated FWE and power for $\alpha = 0.05$, $k = 5$, and $n = 5$.

					True	FWE				Power			
μ_1	μ_2	μ_3	μ_4	μ_5	MED	*TP*	*TH*	*JP*	*JH*	*TP*	*TH*	*JP*	*JH*
Normal Distribution													
0	0	0	0	0	6	0.0494	0.0528	0.0417	0.0400				
0	0	0	0	5	5	0.0526	0.0515	0.0488	0.0407	0.8254	0.9265	0.5596	0.9102
0	0	0	5	5	4	0.0465	0.0527	0.0421	0.0435	0.8380	0.9243	0.5998	0.9054
0	0	5	5	5	3	0.0507	0.0520	0.0448	0.0495	0.8500	0.9222	0.6365	0.8875
0	5	5	5	5	2	0.0512	0.0509	0.0494	0.0466	0.8700	0.9154	0.7009	0.8601
5	5	5	5	5	1	—	—	—	—	0.9483	0.8876	0.8698	0.6729
4	4	4	4	4	1	—	—	—	—	0.8158	0.7001	0.6959	0.4788
0	0	0	4	5	4	0.0503	0.0497	0.0459	0.0429	0.6467	0.8225	0.4503	0.7712
0	0	3	4	5	3	0.0455	0.0413	0.0391	0.0383	0.4264	0.5801	0.3142	0.4905
0	2	3	4	5	2	0.0394	0.0283	0.0382	0.0221	0.2345	0.2828	0.1722	0.2164
1	2	3	4	5	1	—	—	—	—	0.1355	0.0940	0.1139	0.0610
2	3	4	5	4	1	—	—	—	—	0.3462	0.2705	0.2938	0.1777
2	3	4	5	3	1	—	—	—	—	0.3564	0.2745	0.2996	0.1808
2	3	4	5	2	1	—	—	—	—	0.3525	0.2726	0.2881	0.1739
0	3	4	5	4	2	0.0468	0.0400	0.0451	0.0349	0.4909	0.5875	0.3596	0.4837
0	3	4	5	3	2	0.0469	0.0402	0.0444	0.0316	0.4791	0.5721	0.3547	0.4741
0	3	4	5	2	2	0.0458	0.0395	0.0427	0.0307	0.4903	0.5913	0.3660	0.4891
3	4	5	4	3	1	—	—	—	—	0.6322	0.5280	0.5407	0.3484
3	4	5	4	2	1	—	—	—	—	0.6305	0.5277	0.5340	0.3432
0	3	5	3	2	2	0.0465	0.0398	0.0436	0.0332	0.4946	0.5944	0.3725	0.5113
0	3	5	3	1	2	0.0459	0.0391	0.0431	0.0334	0.4930	0.6014	0.3721	0.5208

Average power for true MED = 1										0.5272	0.4444	0.4545	0.3046
Average power for true MED > 1										0.5949	0.6934	0.4382	0.6267
Average power for all cases										0.5678	0.5938	0.4447	0.4979
Cauchy Distribution													
0	0	0	0	0	6	0.0420	0.0452	0.0451	0.0395				
0	0	0	0	5	5	0.0357	0.0349	0.0459	0.0360	0.2351	0.3190	0.3887	0.6883
0	0	0	5	5	4	0.0320	0.0276	0.0435	0.0416	0.2381	0.3103	0.4204	0.6714
0	0	5	5	5	3	0.0326	0.0260	0.0482	0.0465	0.2375	0.2977	0.4201	0.6178
0	5	5	5	5	2	0.0339	0.0231	0.0448	0.0349	0.2647	0.2993	0.4718	0.6025
5	5	5	5	5	1	—	—	—	—	0.3124	0.2501	0.5719	0.4886
4	4	4	4	4	1	—	—	—	—	0.2395	0.1865	0.4972	0.4050
0	0	0	4	5	4	0.0306	0.0248	0.0436	0.0363	0.1664	0.2365	0.3438	0.5826
0	0	3	4	5	3	0.0270	0.0193	0.0412	0.0352	0.1114	0.1503	0.2848	0.4269
0	2	3	4	5	2	0.0261	0.0134	0.0389	0.0232	0.0614	0.0699	0.2054	0.2638
1	2	3	4	5	1	—	—	—	—	0.0511	0.0287	0.1427	0.0931
2	3	4	5	4	1	—	—	—	—	0.1103	0.0694	0.3106	0.2358
2	3	4	5	3	1	—	—	—	—	0.1117	0.0728	0.3103	0.2344
2	3	4	5	2	1	—	—	—	—	0.1041	0.0682	0.3091	0.2355
0	3	4	5	4	2	0.0293	0.0140	0.0421	0.0284	0.1280	0.1444	0.3309	0.4235
0	3	4	5	3	2	0.0275	0.0151	0.0452	0.0319	0.1226	0.1410	0.3310	0.4201
0	3	4	5	2	2	0.0289	0.0155	0.0421	0.0291	0.1288	0.1493	0.3228	0.4240
3	4	5	4	3	1	—	—	—	—	0.1854	0.1307	0.4407	0.3534
3	4	5	4	2	1	—	—	—	—	0.1805	0.1303	0.4403	0.3599
0	3	5	3	2	2	0.0314	0.0183	0.0440	0.0332	0.1248	0.1466	0.3233	0.4344
0	3	5	3	1	2	0.0291	0.0154	0.0426	0.0322	0.1268	0.1522	0.3335	0.4439

(continued)

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Table 5. Continued.

						FWE				Power			
μ_1	μ_2	μ_3	μ_4	μ_5	True MED	*TP*	*TH*	*JP*	*JH*	*TP*	*TH*	*JP*	*JH*
Average power for true MED = 1										0.1619	0.1171	0.3779	0.3007
Average power for true MED > 1										0.1621	0.2014	0.3480	0.4999
Average power for all cases										0.1620	0.1677	0.3600	0.4202
Exponential Distribution													
1	1	1	1	1	6	0.0599	0.0766	0.0428	0.0417				
1	1	1	1	6	5	0.0041	0.0054	0.0451	0.0388	0.7845	0.8968	0.3288	0.5885
1	1	1	6	6	4	0.0004	0.0005	0.0428	0.0371	0.5178	0.6653	0.3527	0.5754
1	1	6	6	6	3	0.0000	0.0002	0.0453	0.0440	0.3574	0.4847	0.3712	0.5405
1	6	6	6	6	2	0.0000	0.0000	0.0477	0.0333	0.2528	0.3144	0.4090	0.5272
6	6	6	6	6	1	—	—	—	—	0.2036	0.1372	0.5426	0.3571
5	5	5	5	5	1	—	—	—	—	0.1768	0.1223	0.4430	0.2884
1	1	1	5	6	4	0.0006	0.0007	0.0431	0.0373	0.4057	0.5555	0.3091	0.5129
1	1	4	5	6	3	0.0001	0.0001	0.0405	0.0342	0.1680	0.2562	0.2523	0.3752
1	3	4	5	6	2	0.0000	0.0000	0.0352	0.0189	0.0423	0.0573	0.1873	0.2439

2	3	4	5	6	1	—	—	—	—	0.0037	0.0014	0.1423	0.0757
3	4	5	6	5	1	—	—	—	—	0.0263	0.0138	0.2814	0.1596
3	4	5	6	4	1	—	—	—	—	0.0342	0.0187	0.2726	0.1560
3	4	5	6	3	1	—	—	—	—	0.0387	0.0219	0.2703	0.1551
1	4	5	6	5	2	0.0001	0.0000	0.0390	0.0245	0.1035	0.1391	0.2650	0.3631
1	4	5	6	4	2	0.0000	0.0000	0.0431	0.0278	0.1270	0.1635	0.2742	0.3599
1	4	5	6	3	2	0.0000	0.0000	0.0382	0.0240	0.1472	0.1878	0.2702	0.3617
4	5	6	5	4	1	—	—	—	—	0.0960	0.0574	0.3925	0.2372
4	5	6	5	3	1	—	—	—	—	0.1087	0.0642	0.3732	0.2289
1	4	6	4	3	2	0.0002	0.0000	0.0402	0.0252	0.1770	0.2294	0.2763	0.3697
1	4	6	4	2	2	0.0000	0.0000	0.0412	0.0260	0.2007	0.2482	0.2779	0.3671
Average power for true MED = 1										0.0860	0.0546	0.3397	0.2073
Average power for true MED > 1										0.2737	0.3499	0.2978	0.4321
Average power for all cases										0.1986	0.2318	0.3146	0.3422

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CONCLUSIONS

In this paper we propose two nonparametric procedures *JP* and *JH* for identifying MED in a one-way layout setting with general dose–response relationship. It is noted that both procedures control the FWE very well under all configurations considered, while the parametric analogues *TP* and *TH* fail to control the Type I error rate strongly for exponential distribution. Moreover, when the normality assumption is violated, we observe that the proposed nonparametric procedures *JP* and *JH* are better than the parametric analogues *TP* and *TH* except for exponential distribution with high doses of true MED. However, from the considerations of both error rate control and power performance, the tests *JP* and *JH* are recommended over tests *TP* and *TH* at identifying the MED for nonnormal data. On average, the powers for *JP* and *JH* tests are about 100–400% of the powers for *TP* and *TH*. In the normal model, *TP* and *TH* perform better than *JP* and *JH* as expected. However, *JP* and *JH* are quite competitive and they achieve averagely about 70–90% of the power for *TP* and *TH*. Finally, we note that this study has restricted to the equal sample size case, and its conclusions need to be generalized to the unequal sample size case, in which the limiting correlations are unequal for pairwise contrasts. However, this can be easily solved since the required critical constants and p-values can be obtained approximately by replacing all correlations with their average.

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