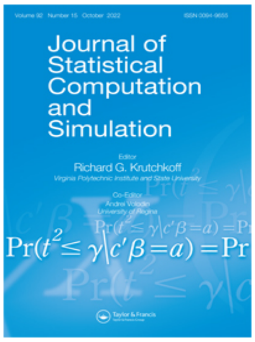


Journal of Statistical Computation and Simulation

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/gscs20

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**To cite this article:** K. Krishnamoorthy, Shanshan Lv & Saptarshi Chakraberty (2022): A new confidence interval for the ratio of two normal means and comparisons, Journal of Statistical Computation and Simulation, DOI: 10.1080/00949655.2022.2117360

**To link to this article:** https://doi.org/10.1080/00949655.2022.2117360

Published online: 15 Sep 2022.

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JOURNAL OF STATISTICAL COMPUTATION AND SIMULATION
https://doi.org/10.1080/00949655.2022.2117360

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# A new confidence interval for the ratio of two normal means and comparisons

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**ABSTRACT**
The problem of estimating the ratio of means of two independent normal distributions is considered. Interval estimation method similar to Welch's approximate degrees of freedom solution for the Behrens–Fisher problem is proposed. The test and confidence interval (CI) for the ratio of means are compared with the available CIs including the one based on the modified likelihood ratio test. Extensive simulation studies indicate that the proposed method is accurate even for very small samples and simpler than other available likelihood-based tests and CIs. The methods are illustrated using an example.

**ARTICLE HISTORY**
Received 2 June 2022
Accepted 22 August 2022

**KEYWORDS**
Coverage probability; exact test; Fieller's theorem; fiducial test; precision

## 1. Introduction

In most applications, two populations are compared using the difference of the means or the medians. Ratio of means is used to compare two populations of positive data. Finney [1] has noted that the relative potency of a new drug to that of a standard one can be assessed in terms of a ratio of means. Berger and Hsu [2] and Chow and Liu [3] have mentioned similar applications of estimates of a ratio of means in bioequivalence study. Many articles on the ratio of means of normal distributions have appeared. Fieller's [4] confidence interval for the ratio of normal means (assuming that the variances are equal) is the most popular and commonly used in applications [5]. Hwang [6] has proposed a resampling approach to construct confidence intervals for the ratio of means. In a meta-analysis setting, Friedrich et al. [7] described a method of combining the ratio of means from each of several independent studies. Applications of estimates of the ratio of means in fluorescence ratio imaging are noted in van Kempen and van Vliet [8]. Confidence estimation for other related problems can be found in George and Kibria [9].

Although, importance and applications of inferential procedures for the ratio of normal means are well understood, only limited results are available when the population variances are unknown and arbitrary. In particular, we note that among solutions for testing or interval estimating the difference between two normal means when the variances are arbitrary (Behrens–Fisher problem), the Welch approximate degrees of freedom solution is accurate and popular, and it is available in some scientific calculators such as the TI-84. Such

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a simple accurate solution is not available for estimating the ratio of two normal means. Wu and Jiang [10] have proposed a modified likelihood ratio test (MLRT) which is highly accurate and satisfactory even for small samples. However, the proposed MLRT is not simple and numerically involved to find a confidence interval for the ratio of means. Lee and Lin [11] have proposed a fiducial CI which is conceptually simple and it can be estimated by Monte Carlo simulation. Recently, Bonett and Price [12] have proposed a simple closed-form CI based on the distribution of log-transformed sample means. However, the available CIs were not evaluated extensively in terms of coverage probability and precision and no comparison study was made.

In this article, we propose a method of computing CIs for the ratio of normal means. Our method is similar to the Welch approximate degrees of freedom solution for estimating the difference between two normal means. In Section 2, we first describe the methods of finding CIs based on the MLRT and fiducial approach. Then we describe the Bonett and Price confidence interval and our method of finding CIs. An algorithm for computing a CI based on our method is also given. In Section 3, we carry out extensive simulation studies by evaluating all interval estimation methods in terms of coverage probability and precision. Accuracy of the methods is also evaluated in terms of type I error rates. An illustrative example based on real life data is given in Section 4. Some concluding remarks are given in Section 5.

## 2. Confidence intervals for the ratio of means

Let $(\bar{X}_i, S_i^2)$ denote the (mean, variance) based on a sample of size $n_i$ from a normal distribution with mean $\mu_i$ and variance $\sigma_i^2$, $N(\mu_i, \sigma_i^2)$, $i = 1, 2$. When $\sigma_1^2 = \sigma_2^2$, a CI for $\theta$ can be obtained based on the pivotal quantity given by

$$T_e(\theta) = \frac{\bar{X}_1 - \theta\bar{X}_2}{S_p\sqrt{\frac{1}{n_1} + \frac{\theta^2}{n_2}}}, \tag{1}$$

where the pooled sample variance $S_p^2 = (m_1S_1^2 + m_2S_2^2)/(m_1 + m_2)$, and $m_i = n_i - 1$. The quantity $T_e(\theta)$ has the $t$ distribution with degrees of freedom (df) $m = m_1 + m_2$. A two-sided $100\,(1-\alpha)\%$ CI for $\theta$ are formed by the roots of the equation $|T_e(\theta)| = t_{m;1-\alpha/2}$, where $t_{m;q}$ denotes the $100\,q$ percentile of the $t$ distribution with df = $m$. The CI formed by these roots is given by

$$\frac{\bar{X}_1\bar{X}_2 \;\pm\; t_{m;1-\alpha/2}S_p\sqrt{\frac{\bar{X}_1^2}{n_2} + \frac{1}{n_1}\left(\bar{X}_2^2 - t_{m;1-\alpha/2}^2\frac{S_p^2}{n_2}\right)}}{\bar{X}_2^2 - t_{m;1-\alpha/2}^2\frac{S_p^2}{n_2}}. \tag{2}$$

The above exact CI is based on Fieller's [4] results, and is commonly referred to as the Fieller CI.

**Remark 2.1:** Applying the result that $a^2 - b^2 = (a-b)(a+b)$ to the term within the brackets under the radical sign in the above formula (2), we see that the above CI is defined and positive if the lower bound $\bar{X}_2 - t_{m;1-\alpha/2}S_p/n_2$ for $\mu_2$ is positive. By interchanging the subscripts 1 and 2 in the above formula, we find a CI for the ratio $\theta_2/\theta_1 = \theta^{-1}$. This CI for $\theta^{-1}$ is defined if the lower bound $\bar{X}_1 - t_{m;1-\alpha/2}S_p/n_1$ for $\mu_1$ is positive. Thus, the above CI is defined and positive if both $100(1-\alpha/2)\%$ lower bounds for $\mu_1$ and $\mu_2$ are positive.

In the following sections, we shall describe four different approaches of finding CIs for the ratio of means when the variances are unknown and arbitrary.

### 2.1. Confidence intervals based on the MLRT

For a given data from the $i$th population, let $(\bar{x}_i, s_i^2)$ denote the (mean, variance) based on the data. To describe the MLRT by Wu and Jiang [10], write the MLEs

$$\widehat{\theta} = \frac{\bar{x}_1}{\bar{x}_2}, \quad \widehat{\mu}_2 = \bar{x}_2, \quad \text{and} \quad \widehat{\sigma}_i^2 = \frac{1}{n_i}\sum_{i=1}^{n_i}(x_{ij} - \bar{x}_i)^2, \quad i = 1, 2.$$

The constrained MLEs when $\theta$ is fixed are given by the recursive equations

$$\begin{aligned}
\widehat{\mu}_{2\theta} &= \left(\frac{n_1\theta\bar{x}_1}{\widehat{\sigma}_{1\theta}^2} + \frac{n_2\bar{x}_2}{\widehat{\sigma}_{2\theta}^2}\right) \Big/ \left(\frac{n_1\theta^2}{\widehat{\sigma}_{1\theta}^2} + \frac{n_2}{\widehat{\sigma}_{2\theta}^2}\right), \\
\widehat{\sigma}_{1\theta}^2 &= \widehat{\sigma}_1^2 + (\bar{x}_1 - \theta\widehat{\mu}_{2\theta})^2, \\
\widehat{\sigma}_{2\theta}^2 &= \widehat{\sigma}_2^2 + (\bar{x}_2 - \widehat{\mu}_{2\theta})^2.
\end{aligned} \tag{3}$$

The LRT statistic is given by

$$r(\theta) = \text{sgn}(\widehat{\theta} - \theta)\left\{n_1 \ln\frac{\widehat{\sigma}_{1\theta}^2}{\widehat{\sigma}_1^2} + n_2 \ln\frac{\widehat{\sigma}_{2\theta}^2}{\widehat{\sigma}_2^2}\right\}^{1/2}. \tag{4}$$

To write the MLRT statistic, define

$$\begin{aligned}
u(\theta) = \sqrt{n_1n_2}&\left[\frac{\widehat{\theta}\widehat{\mu}_2 - \theta\widehat{\mu}_{2\theta}}{\widehat{\sigma}_1^2\widehat{\sigma}_{2\theta}^2} + \frac{\theta(\widehat{\mu}_{2\theta} - \widehat{\mu}_2)}{\widehat{\sigma}_{1\theta}^2\widehat{\sigma}_2^2}\right]\left(\frac{\widehat{\sigma}_1^3\widehat{\sigma}_2^3}{\widehat{\sigma}_{1\theta}^2\widehat{\sigma}_{2\theta}^2}\right) \\
&\times\left\{\frac{n_1\theta^2}{\widehat{\sigma}_{1\theta}^2}\left(\frac{2\widehat{\sigma}_1^2}{\widehat{\sigma}_{1\theta}^2} - 1\right) + \frac{n_2}{\widehat{\sigma}_{2\theta}^2}\left(\frac{2\widehat{\sigma}_2^2}{\widehat{\sigma}_{2\theta}^2} - 1\right)\right\}^{-1/2}.
\end{aligned} \tag{5}$$

Finally, the MLRT statistic is expressed as

$$r^*(\theta) = r(\theta) + \frac{1}{r(\theta)}\ln\frac{u(\theta)}{r(\theta)} \tag{6}$$

and is approximately standard normally distributed with an error of $O(n^{-3/2})$.

A CI for $\theta$ can be obtained by inverting the MLRT. The lower and upper bounds of a $100(1-\alpha)\%$ CI are the roots of the equations

$$r^*(\theta) - z_{1-\alpha/2} = 0 \quad \text{and} \quad r^*(\theta) + z_{1-\alpha/2} = 0, \tag{7}$$

respectively, where $z_p$ denotes the $100p$ percentile of the standard normal distribution. Using the endpoints of the CI in (10) as the starting value, a bisection method can be used to find the roots of the above equations.

### 2.2. Fiducial confidence intervals

To find a fiducial CI for the ratio of means, we first need to find fiducial distributions for the parameters of a normal distribution. A fiducial distribution of a parameter is regarded as the posterior distribution of the parameter without assuming a prior distribution [13]. Fiducial distributions for normal parameters can be readily obtained using Dawid and Stone's [14] functional model stochastic relation. Let $(\bar{x}, s^2)$ be an observed value of $(\bar{X}, S^2)$, which is based on a sample of size $n$. Notice that $\bar{X} \stackrel{d}{=} \mu + Z\frac{\sigma}{\sqrt{n}}$ and $S^2 \stackrel{d}{=} \sigma^2 \frac{\chi^2_m}{m}$, where $Z \sim N(0,1)$ independently of $\chi^2_m$, $m = n-1$, and $X \stackrel{d}{=} Y$ means that $X$ and $Y$ are identically distributed. Solving the these "equations" for $\mu$ and $\sigma^2$ and then replacing $(\bar{X}, S^2)$ with $(\bar{x}, s^2)$, we obtain the fiducial quantities (FQs) for the parameters $\mu$ and $\sigma^2$ as

$$Q_\mu = \bar{x} + \frac{Z}{U}\frac{s}{\sqrt{n}} \quad \text{and} \quad Q_{\sigma^2} = \frac{s^2}{U^2}, \tag{8}$$

where $U^2 = \chi^2_m/m$. That is, for a given $(\bar{x}, s^2)$, the distribution of $Q_\mu$ is called the fiducial distribution of $\mu$ and the distribution of $s^2/U^2$ is the fiducial distribution for $\sigma^2$.

For the two-sample problem, let $(\bar{x}_i, s_i)$ be an observed value of $(\bar{X}_i, S_i)$, $i = 1, 2$. Furthermore, let $\widetilde{s}_i = s_i/\sqrt{n_i}$ be an observed value of $\widetilde{S}_i = S_i/\sqrt{n_i}$, $i = 1, 2$. A FQ for the ratio $\theta = \mu_1/\mu_2$ can be obtained by substitution as

$$Q_\theta = \frac{Q_{\mu_1}}{Q_{\mu_2}} = \frac{\bar{x}_1 + \frac{Z_1}{U_1}\widetilde{s}_1}{\bar{x}_2 + \frac{Z_2}{U_2}\widetilde{s}_2}, \tag{9}$$

where $Z_i$'s are $U_i$'s are mutually independent with $Z_i \sim N(0,1)$ and $m_i U_i^2 \sim \chi^2_{m_i}$ distribution. It should be noted that Lee and Lin [11] have obtained the same FQ $Q_\theta$ using the generalized variable approach by Weerahandi [15], which is a special case of the fiducial approach [16]. Krishnamoorthy and Mathew [17] have used this generalized variable approach to find a CI for the ratio of log-normal means. For a given $(\bar{x}_1, s_1, \bar{x}_2, s_2)$ the distribution of $Q_\theta$ in (9) does not depend on any parameter and so its percentiles can be estimated by Monte Carlo simulation. The lower and upper $100\,\alpha$ percentiles form a $100(1-2\alpha)\%$ fiducial CI for $\theta$ (see Lee and Lin [11]).

The percentiles $Q_\theta$ can also be approximated using the modified normal-based approximation given in Krishnamoorthy [18] as follows. Let $Q_{\mu_i} = \bar{x}_i + \frac{Z_i}{U_i}\widetilde{s}_i$, and notice that $Z_i/U_i \sim t_{m_i}$, $t$ distribution with degrees of freedom (df) $m_i = n_i - 1, i = 1, 2$. So $E(Q_{\mu_i}) = \bar{x}_i$ and $Q_{\mu_i, 1-\alpha} = \bar{x}_i + t_{m_i;1-\alpha}\widetilde{s}_i$ is the $100\,(1-\alpha)$ percentile of $Q_{\mu_i}$, $i = 1, 2$. Then, an approximate $100\,(1-2\alpha)\%$ fiducial CI for $\theta$ is given by

$$\frac{\bar{x}_1\bar{x}_2 \pm \left\{t^2_{m_2;1-\alpha}\widetilde{s}^2_2\left(\bar{x}^2_1 - \frac{1}{2}t^2_{m_1;1-\alpha}\widetilde{s}^2_1\right) + t^2_{m_1;1-\alpha}\widetilde{s}^2_1\left(\bar{x}^2_2 - \frac{1}{2}t^2_{m_2;1-\alpha}\widetilde{s}^2_2\right)\right\}^{\frac{1}{2}}}{\left[\bar{x}^2_2 - t^2_{m_2;1-\alpha}\widetilde{s}^2_2\right]}, \tag{10}$$

where $\widetilde{s}^2_i = s^2_i/n_i$, $i = 1, 2$. For example, using $\alpha = 0.025$ in the above expression, we find an approximate 95% fiducial CI for $\theta$. It can be shown, along the lines of Remark 1, the above CI is positive if both $100(1-\alpha/2)\%$ lower bounds for $\mu_1$ and $\mu_2$ are positive.

### 2.3. Confidence intervals based on log-transformation

Bonett and Price [12] have noted that the sampling distribution of $\ln(\bar{X}_1/\bar{X}_2)$ should converge to normality faster than the sampling distribution of $\bar{X}_1/\bar{X}_2$. Using a delta method an estimate of the variance can be found as $\widehat{\mathrm{var}}((\ln(\bar{X}_1/\bar{X}_2)) = \frac{\widetilde{S}_1^2}{\bar{X}_1^2} + \frac{\widetilde{S}_2^2}{\bar{X}_2^2}$. Using this variance estimate, an approximate CI for $\theta$ can be obtained as

$$\exp\left\{\ln\left(\bar{X}_1/\bar{X}_2\right) \pm t_{f^*;1-\alpha/2}\sqrt{\widehat{\mathrm{var}}(\ln(\bar{X}_1/\bar{X}_2))}\right\}, \tag{11}$$

where the degrees of freedom

$$f^* = \left(\frac{\widetilde{S}_1^2}{\bar{X}_1^2} + \frac{\widetilde{S}_2^2}{\bar{X}_2^2}\right)^2 \Big/ \left[\frac{\widetilde{S}_1^4}{m_1\bar{X}_1^4} + \frac{\widetilde{S}_2^4}{m_2\bar{X}_2^4}\right],$$

is a Satterthwaite approximate degrees of freedom.

### 2.4. Welch's approximate degrees of freedom method

The Welch method to find a CI for the difference $\mu_1 - \mu_2$ is based on an approximate distribution of $\widehat{\mathrm{var}}(\bar{X}_1 - \bar{X}_2) = \widetilde{S}_1^2 + \widetilde{S}_2^2$. Let us find a CI for $\theta$ based on the quantity

$$T(\theta) = \frac{\bar{X}_1 - \theta\bar{X}_2}{\sqrt{\widetilde{S}_1^2 + \theta^2\widetilde{S}_2^2}}. \tag{12}$$

When the variances are unknown and arbitrary, it is not possible to find an exact distribution of $T(\theta)$, and so we approximate its distribution along the lines of Welch's method to find a CI for the difference between two means. In particular, we approximate the distribution of

$$W = \frac{\widetilde{S}_1^2 + \theta^2\widetilde{S}_2^2}{\widetilde{\sigma}_1^2 + \theta^2\widetilde{\sigma}_2^2}$$

by the distribution of $\chi_f^2/f$, where $\widetilde{\sigma}_i^2 = \sigma_i^2/n_i$, $i = 1, 2$, and $f$ is determined so that the variance of $W$ is equal to $\mathrm{var}(\chi_f^2/f) = 2/f$. Noting that

$$\mathrm{var}(W) = \frac{2\frac{\widetilde{\sigma}_1^4}{m_1} + 2\theta^4\frac{\widetilde{\sigma}_2^4}{m_2}}{\left(\widetilde{\sigma}_1^2 + \theta^2\widetilde{\sigma}_2^2\right)^2},$$

we estimate the variance by $\widehat{\mathrm{var}}(W)$, which is obtained by replacing $(\widetilde{\sigma}_1^2, \widetilde{\sigma}_2^2)$ by $(\widetilde{S}_1^2, \widetilde{S}_2^2)$. Equating the $\widehat{\mathrm{var}}(W)$ to the variance of $\chi_f^2/f$ and solving the resulting equation for $f$, we find

$$f = f(\theta) = \frac{\left(\widetilde{S}_1^2 + \theta^2 \widetilde{S}_2^2\right)^2}{\frac{\widetilde{S}_1^4}{m_1} + \theta^4 \frac{\widetilde{S}_2^4}{m_2}}.$$

Thus, $W \sim \chi^2_{f(\theta)}/f(\theta)$, and using the standard stochastic representation of the Student $t$ random variable, we see that

$$T(\theta) = \frac{\bar{X}_1 - \theta \bar{X}_2}{\sqrt{\widetilde{S}_1^2 + \theta^2 \widetilde{S}_2^2}} \sim t_{f(\theta)}, \quad \text{approximately.} \tag{13}$$

**Remark 2.2:** As in the Welch approximate degrees of freedom solution to the Behrens–Fisher problem, we can show that the df $f(\theta)$ satisfies $\min\{m_1, m_2\} < f(\theta) \le m_1 + m_2$. To show this, we find the derivative $f'(\theta)$ that can be expressed as

$$f'(\theta) = \frac{4\widetilde{S}_1^2 \widetilde{S}_2^2 \theta (\widetilde{S}_1^2 + \widetilde{S}_2^2 \theta^2) \left( \frac{\widetilde{S}_1^2}{m_1} - \frac{\widetilde{S}_2^2 \theta^2}{m_2} \right)}{\left( \frac{\widetilde{S}_1^4}{m_1} + \frac{\widetilde{S}_2^4 \theta^4}{m_2} \right)^2},$$

where $\widetilde{S}_1^2 = S_1^2/n_1$ and $\widetilde{S}_2^2 = S_2^2/n_2$. Note that $f'(\theta) = 0$ at $\theta = \theta^* = [(\frac{\widetilde{S}_1^2}{m_1}) \Big/ (\frac{\widetilde{S}_2^2}{m_2})]^{1/2}$, negative for $\theta > \theta^*$ and is positive for $\theta < \theta^*$. Thus, $f(\theta)$ attains the maximum at $\theta = \theta^*$ and $f(\theta^*) = m_1 + m_2$. Furthermore, $f(\theta) \to m_1$ when $\theta \to 0$ and it approaches $m_2$ when $\theta \to \infty$. So $\min\{m_1, m_2\} \le f(\theta) < m_1 + m_2$ for all $\theta > 0$.

#### 2.4.1. Confidence interval based on the approximate degrees of freedom $f(\widehat{\theta})$

Let $\widehat{\theta} = \bar{X}_1/\bar{X}_2$. Using (13) with $f(\theta)$ replaced by $f(\widehat{\theta})$, we can obtain the following 100 $(1 - \alpha)$% confidence set as

$$\left\{ \theta : -t_{f(\widehat{\theta});1-\alpha/2} \le T(\theta) \le t_{f(\widehat{\theta});1-\alpha/2} \right\},$$

where

$$f(\widehat{\theta}) = \frac{\left(\bar{X}_2^2 \widetilde{S}_1^2 + \bar{X}_1^2 \widetilde{S}_2^2\right)^2}{\bar{X}_2^4 \frac{\widetilde{S}_1^4}{m_1} + \bar{X}_1^4 \frac{\widetilde{S}_2^4}{m_2}}. \tag{14}$$

It can be readily verified that the above confidence set is the interval

$$\frac{\bar{X}_1 \bar{X}_2 \pm t_{f(\widehat{\theta});1-\alpha/2} \sqrt{\widetilde{S}_1^2 \left( \bar{X}_2^2 - \frac{1}{2} t^2_{f(\widehat{\theta});1-\alpha/2} \widetilde{S}_2^2 \right) + \widetilde{S}_2^2 \left( \bar{X}_1^2 - \frac{1}{2} t^2_{f(\widehat{\theta});1-\alpha/2} \widetilde{S}_1^2 \right)}}{\bar{X}_2^2 - t^2_{f(\widehat{\theta});1-\alpha/2} \widetilde{S}_2^2}. \tag{15}$$

Along the lines of Remark 1, it can be shown that the above CI is a bona fide positive interval if $\bar{X}_i - \frac{1}{\sqrt{2}} t_{f(\widehat{\theta});1-\alpha/2} \widetilde{S}_i > 0$ for $i = 1, 2$. Note that this quantity $\bar{X}_i - \frac{1}{\sqrt{2}} t_{f(\widehat{\theta});1-\alpha/2} \widetilde{S}_i$ is larger than the 100 $(1 - \alpha/2)$% lower confidence limit for $\mu_i$ based on the df $f(\widehat{\theta})$.

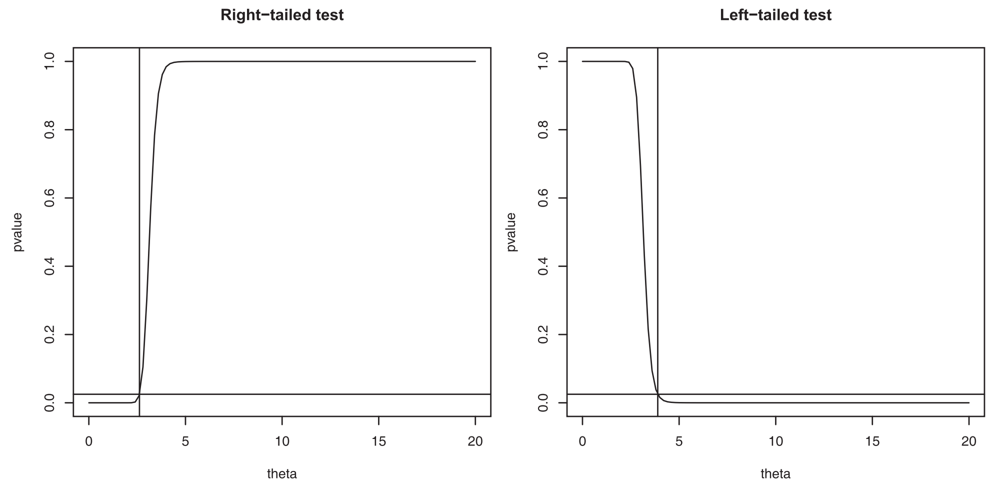


**Figure 1.** *P*-values in (16) and (17) as a function of $\theta$ when $(n_1, n_2) = (20, 15)$, $(\bar{x}_1, \bar{x}_2) = (6.079, 1.932)$ and $(s_1^2, s_2^2) = (1.035, 0.4139)$; the right-tailed test produced 2.5% lower bound as 2.619 and the left-tailed test produced 2.5% upper bound as 3.894.

### *2.4.2. A confidence interval based on $f(\theta)$*

A CI for $\theta$ can be obtained by inverting one-sided tests. Consider testing $H_0 : \theta = \theta_0$ vs. $H_a : \theta > \theta_0$. The lower bound of the 100 $(1-\alpha)$% CI is obtained by inverting a right-tailed test or obtained as the value of $\theta_0$ that satisfies the equation (see Figure 1)

$$P_{R_t;\alpha}(\theta_0) = P\left(t_{f(\theta_0)} > \frac{\bar{x}_1 - \theta_0 \bar{x}_2}{\sqrt{\tilde{s}_1^2 + \theta_0^2 \tilde{s}_2^2}}\right) - \frac{\alpha}{2} = 0, \tag{16}$$

where $(\bar{x}_i, s_i^2)$ is an observed value of $(\bar{X}_i, S_i^2)$, $i = 1, 2$. Similarly, the corresponding upper bound can be obtained as the value of $\theta_0$ that satisfies the equation (see Figure 1)

$$P_{L_t,\alpha}(\theta_0) = P\left(t_{f(\theta_0)} < \frac{\bar{x}_1 - \theta_0 \bar{x}_2}{\sqrt{\tilde{s}_1^2 + \theta_0^2 \tilde{s}_2^2}}\right) - \frac{\alpha}{2} = 0. \tag{17}$$

The lower and upper bounds form a 100 $(1-\alpha)$% CI for $\theta$ and we refer to this CI as the Welch CI. These confidence bounds can be found using the following algorithm.

**Algorithm 2.1:** (1) For a given $(\bar{x}_1, \tilde{s}_1, \bar{x}_2, \tilde{s}_2)$ and the confidence level $1-\alpha$, find the approximate CI $(L, U)$ in (15).

(2) If $P_{R_t,\alpha}(L) < 0$, find $\delta > 0$ so that $P_{R_t,\alpha}(L+\delta) > 0$ and the root bracketing interval is $(L, L+\delta)$; else find $\delta > 0$ so that $P_{R_t,\alpha}(L-\delta) < 0$ and the root bracketing interval is $(L-\delta, L)$; see Figure 1.

(3) Using a bisection method with this root bracketing interval, find the lower bound as the root of Equation (16).

(4) If $P_{L_t,\alpha}(U) > 0$, find $\delta > 0$ so that $P_{R_t,\alpha}(U+\delta) < 0$ and the root bracketing interval is $(U, U+\delta)$; else if $P_{L_t,\alpha}(U) < 0$, find $\delta > 0$ so that $P_{R_t,\alpha}(U-\delta) < 0$. Then the root bracketing interval is $(U-\delta, U)$; see Figure 1.

(5) Using the bracketing interval and a bisection method, find the upper bound as the root of Equation (17).

The two roots found in the above algorithm are the endpoints of a 100 $(1-\alpha)$% Welch CI for $\theta$.

## 3. Coverage and comparison studies

To judge the accuracy of the CIs for the ratio of normal means when the variances are unknown and arbitrary, we estimated the coverage probabilities and expected widths of the CIs and type I error rates of the tests for some parameters and sample sizes. All Monte Carlo estimates are based on 100,000 simulation runs. In situations where the ratio of means is an appropriate measure of difference, the variable is usually positive. For a normal population, the ratio of the mean to the standard deviation has to be on the order of three or more, for the probability of a negative value is negligible. That is, in practical situations where the ratio of means needs to be estimated, the mean $\mu$ must be at least $3\sigma$. This has been noted by Johnson and Welch [19] in the problem of estimating the coefficient of variation of a normal population. So in our simulation study, samples were generated from a $N(\mu_i, \sigma_i^2)$ distribution with $\mu_i \geq 3\sigma_i$, $i = 1, 2$. Furthermore, all interval estimation methods are scale invariant, and so without loss of generality, we choose $\sigma_1 = 1.0$ and $\sigma_2 = .01, .05, .1, .3, .5, .8, .9, .95$ and .99.

In Table 1, we reported type I error rates of the tests 1 = Bonnet and Price, 2 = fiducial test, 3 = test based on $f(\widehat{\theta})$, and 4 = Welch test for some small samples. The MLRT is not included for comparison, because for some small samples the term under the square root in (5) could be negative and we can't compute its type I error rates accurately. The reported type I error rates in Table 1 indicate that the fiducial test controls the type I error rates within the nominal level, but could be conservative when the variances are not drastically different. Bonett and Price's test also controls the type I error rates, the error rates are unbalanced with right-tail error rates larger than the corresponding left-tail error rates. These results indicate that the Bonett and Price test is liberal for left-sided hypotheses and conservative for right-sided hypotheses. Tests 3 and 4 control the type I error rates well and the error rates are very close to the nominal level 0.05 for most cases, except when $n_1 = n_2 = 4$. Even for this case, the type I error rates are in the range 0.043 –0.050. Both tests 3 and 4 show improved performance when $n_1 = 4$ and $n_2 = 8$. The Welch test performs like an exact test in controlling type I error rates when $n_1 = 4$ and $n_2 = 8$.

As the type I error rates of the tests are not similar, we can't make a fair comparison of tests with respect to power. However, we compare them in terms of coverage probability and precision. Note that a test based on a CI with higher precision is more powerful than the one based on a CI with lower precision provided both CIs have coverage probabilities close to the nominal level. In Table 2, we presented the coverage probabilities and the expected widths of 95% CIs based on the fiducial, MLRT and the Welch method. We observe from the table values that the Welch CI and the CI based on the MLRT are practically the same in terms of coverage probability and expected width. The fiducial CIs are in general conservative, and it is as good as the other two CIs only when the population variances are very different.

**Table 1.** Left (L) and right-tail (R) type I error rates of the tests when $\alpha = 0.05$.

| | $(n_1, n_2) = (4, 4)$ | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | $(\mu_1, \mu_2) = (3, 3)$ | | | | $(\mu_1, \mu_2) = (4.5, 3)$ | | | |
| $\sigma_1 = 1$ | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 |
| $\sigma_2$ | L(R) | L(R) | L(R) | L(R) | L(R) | L(R) | L(R) | L(R) |
| .01 | .035(.061) | .050(.051) | .050(.050) | .051(.051) | .041(.059) | .050(.050) | .050(.051) | .050(.050) |
| .05 | .035(.062) | .050(.050) | .050(.050) | .050(.051) | .040(.060) | .049(.048) | .049(.051) | .050(.051) |
| .10 | .035(.064) | .048(.048) | .049(.052) | .051(.051) | .042(.059) | .048(.046) | .051(.052) | .052(.051) |
| .30 | .037(.061) | .040(.040) | .049(.053) | .052(.052) | .040(.054) | .035(.035) | .046(.049) | .050(.049) |
| .50 | .035(.054) | .034(.034) | .045(.049) | .049(.048) | .039(.046) | .030(.031) | .042(.046) | .046(.046) |
| .80 | .037(.045) | .030(.029) | .043(.045) | .044(.045) | .044(.038) | .029(.030) | .045(.042) | .046(.045) |
| .90 | .038(.042) | .029(.029) | .042(.044) | .043(.045) | .046(.037) | .029(.030) | .046(.043) | .045(.045) |
| .95 | .038(.040) | .028(.029) | .042(.044) | .045(.044) | .048(.037) | .030(.032) | .046(.043) | .045(.045) |
| .99 | .040(.039) | .028(.028) | .043(.042) | .044(.044) | .049(.034) | .030(.033) | .047(.042) | .045(.046) |
| | $(n_1, n_2) = (4, 8)$ | | | | | | | |
| | $(\mu_1, \mu_2) = (3, 3)$ | | | | $(\mu_1, \mu_2) = (6, 3)$ | | | |
| | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 |
| $\sigma_2$ | L(R) | L(R) | L(R) | L(R) | L(R) | L(R) | L(R) | L(R) |
| .01 | .035(.063) | .050(.052) | .049(.050) | .050(.052) | .043(.056) | .050(.050) | .050(.050) | .050(.050) |
| .05 | .036(.062) | .050(.050) | .050(.050) | .050(.050) | .042(.057) | .050(.049) | .050(.051) | .051(.050) |
| .10 | .035(.062) | .050(.049) | .050(.051) | .051(.050) | .043(.058) | .049(.047) | .050(.052) | .052(.050) |
| .30 | .037(.066) | .047(.046) | .050(.056) | .051(.053) | .046(.059) | .041(.041) | .051(.056) | .054(.053) |
| .50 | .038(.064) | .042(.043) | .049(.057) | .052(.053) | .044(.052) | .036(.035) | .045(.052) | .050(.049) |
| .80 | .038(.058) | .037(.037) | .046(.055) | .051(.050) | .047(.043) | .034(.032) | .046(.049) | .048(.045) |
| .90 | .038(.054) | .036(.035) | .045(.054) | .051(.050) | .048(.042) | .033(.033) | .045(.048) | .047(.047) |
| .95 | .038(.054) | .035(.036) | .044(.054) | .050(.051) | .049(.040) | .034(.034) | .045(.048) | .048(.047) |
| .99 | .039(.052) | .035(.036) | .044(.053) | .049(.050) | .050(.038) | .032(.035) | .046(.046) | .046(.048) |

1 = Bonett and Price test; 2 = Fiducial test; 3 = Test based on $f(\widehat{\theta})$; 4 = Welch test

In Table 3, we reported coverage probabilities, left- and right-tail non-coverage error rates and the expected widths of the Bonett and Price CI, the CI based on the df $f(\widehat{\theta})$ and the Welch CI. Confidence interval based on the MLRT is not included as it is very similar to the Welch CI based on the df $f(\theta)$. For simulation studies, we have considered the sample sizes ranging from 5 to 60, and $(\mu_1, \mu_2) = (3, 3)$ and (9, 3). We first observe from the reported values in Table 3 that the Bonett and Price CI is slightly conservative with unbalanced tail error rates. Thus we can't use the endpoints of the Bonnet and Price two-sided CIs as one-sided lower or upper confidence limits. For example, if we use the right endpoint of a 90% CI based on the Bonett and Price method as a 95% upper confidence limit, then it could be conservative. This Bonnet and Price CI is expected to be shorter than the other two CIs when the variances are not very much different. But in other cases, Bonnet and Price CI is expected to be wider than the other two CIs. The Bonnet and Price CI can be safely used when both sample sizes are 30 or more. The CI based on the df $f(\widehat{\theta})$ and the Welch CI based on the df $f(\theta)$ exhibit similar performances for all cases. Both perform like an exact CI controlling coverage probabilities very close to the nominal level 0.95 while maintaining balanced non-coverage tail error rates and having similar expected widths for all cases. Since the approximate CI based on $f(\widehat{\theta})$ is in closed-form and straightforward to compute, this CI can be recommended in applications.

**Table 2.** Coverage probabilities and (expected widths) of 95% CIs for the ratio of means.

| | $(\mu_1, \mu_2) = c(3, 3)$ | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| $\sigma_1 = 1$ | Fiducial | MLRT | Welch | Fiducial | MLRT | Welch | Fiducial | MLRT | Welch |
| $\sigma_2$ | $(n_1, n_2) = (5, 10)$ | | | $(n_1, n_2) = (10, 10)$ | | | $(n_1, n_2) = (10, 20)$ | | |
| .01 | .949(.464) | .948(.463) | .949(.464) | .950(.464) | .950(.463) | .950(.464) | .950(.463) | .949(.462) | .950(.463) |
| .05 | .951(.466) | .950(.463) | .950(.464) | .951(.465) | .950(.463) | .951(.464) | .950(.465) | .950(.463) | .950(.465) |
| .10 | .953(.472) | .950(.466) | .950(.466) | .951(.467) | .950(.464) | .951(.465) | .951(.465) | .950(.464) | .951(.465) |
| .30 | .963(.534) | .949(.495) | .950(.497) | .955(.489) | .949(.478) | .949(.477) | .952(.475) | .950(.470) | .950(.470) |
| .50 | .970(.652) | .951(.583) | .953(.584) | .960(.531) | .950(.506) | .951(.507) | .955(.493) | .950(.483) | .949(.482) |
| .80 | .970(.984) | .949(.893) | .950(.886) | .964(.630) | .951(.589) | .952(.591) | .957(.538) | .949(.518) | .949(.517) |
| .90 | .969(1.11) | .950(1.01) | .950(1.01) | .963(.672) | .950(.628) | .951(.630) | .957(.557) | .948(.534) | .948(.533) |
| .95 | .968(1.50) | .949(1.40) | .949(1.40) | .964(.696) | .949(.651) | .951(.653) | .959(.567) | .949(.542) | .949(.542) |
| .99 | .967(1.22) | .947(1.11) | .947(1.11) | .964(.718) | .949(.672) | .950(.674) | .960(.578) | .950(.552) | .951(.551) |
| | $(\mu_1, \mu_2) = c(4.5, 3)$ | | | | | | | | |
| .01 | .950(.463) | .949(.462) | .950(.463) | .948(.464) | .948(.462) | .948(.463) | .950(.463) | .949(.461) | .950(.463) |
| .05 | .952(.468) | .949(.464) | .950(.465) | .951(.465) | .950(.463) | .950(.464) | .949(.465) | .949(.463) | .949(.464) |
| .10 | .955(.482) | .950(.470) | .950(.470) | .952(.470) | .951(.466) | .951(.466) | .952(.466) | .950(.464) | .951(.465) |
| .30 | .968(.603) | .949(.541) | .951(.545) | .959(.515) | .950(.495) | .950(.494) | .953(.487) | .949(.479) | .948(.477) |
| .50 | .970(.807) | .951(.722) | .952(.717) | .964(.597) | .951(.559) | .952(.561) | .959(.526) | .951(.508) | .951(.507) |
| .80 | .967(1.30) | .948(1.21) | .947(1.20) | .963(.772) | .951(.723) | .952(.725) | .962(.610) | .952(.580) | .952(.580) |
| .90 | .964(1.47) | .948(1.36) | .946(1.36) | .962(.847) | .949(.797) | .950(.798) | .961(.645) | .949(.613) | .949(.614) |
| .95 | .962(1.64) | .947(1.53) | .945(1.53) | .963(.884) | .950(.834) | .951(.835) | .961(.663) | .950(.630) | .951(.631) |
| .99 | .961(2.01) | .946(1.90) | .943(1.91) | .962(.925) | .950(.875) | .951(.876) | .960(.683) | .950(.648) | .951(.650) |
| | $(\mu_1, \mu_2) = c(9, 3)$ | | | | | | | | |
| .01 | .952(.465) | .951(.463) | .952(.464) | .950(.464) | .950(.463) | .950(.464) | .949(.464) | .948(.463) | .949(.464) |
| .05 | .957(.482) | .951(.470) | .952(.470) | .954(.470) | .951(.466) | .951(.467) | .950(.466) | .949(.464) | .949(.465) |
| .10 | .964(.528) | .950(.491) | .952(.493) | .955(.487) | .950(.477) | .950(.476) | .952(.474) | .949(.470) | .949(.469) |
| .30 | .970(.877) | .950(.790) | .950(.782) | .964(.637) | .950(.593) | .951(.596) | .958(.547) | .949(.524) | .949(.523) |
| .50 | .964(1.36) | .949(1.28) | .947(1.26) | .962(.864) | .950(.814) | .951(.816) | .961(.667) | .951(.633) | .952(.634) |
| .80 | .958(2.43) | .949(2.33) | .946(2.34) | .959(1.29) | .951(1.25) | .951(1.24) | .960(.901) | .952(.865) | .952(.867) |
| .90 | .956(3.13) | .947(3.01) | .947(3.04) | .957(1.45) | .950(1.41) | .950(1.40) | .958(.989) | .950(.954) | .951(.956) |
| .95 | .953(3.03) | .945(2.90) | .948(2.94) | .957(1.54) | .951(1.50) | .950(1.50) | .957(1.03) | .950(1.00) | .950(1.00) |
| .99 | .952(3.84) | .944(3.71) | .946(3.76) | .955(1.63) | .949(1.59) | .949(1.59) | .957(1.08) | .950(1.04) | .950(1.05) |

## 4. Example

This example is taken from Wu and Jiang [10]. In a bioequivalence study of two formulations of a drug product a standard $2 \times 2$ crossover experiment was conducted with 25 subjects to compare a new test formulation with a reference formulation. An objective of the study is to estimate the pharmacokinetics parameters specifying the bioavailability of each formulation, such as the area under the plasma concentration–time curve (AUC) and the maximum plasma concentration (Cmax). Typically, 90% confidence intervals for the ratio of the population means of the test and reference formulations for both AUC and Cmax are used to assess the average bioequivalence of two formulations. For illustration purpose, we shall use the Cmax data that fit a normal distribution [10]. The Cmax data are reproduced here in Table 4.

The sample statistics are obtained as

$$n_1 = 12, \quad \bar{x}_1 = 32.78, \quad s_1^2 = 72.24, \quad n_2 = 13, \quad \bar{x}_2 = 28.70 \quad \text{and} \quad s_2^2 = 36.49.$$

Confidence intervals for the ratio $\theta$ of the means of the test formulation to the reference formulation by various methods are given in Table 5. To test the hypotheses $H_0 : \theta = 1$ vs. $H_a : \theta \neq 1$ using the Welch method, we computed the statistic $T(\theta_0)$ as 1.3760, the degrees of freedom as 19.72 and the $p$-value as $2[1 - P(t_{19.72} > 1.3760)] = 0.1842$. To apply the

**Table 3.** Left-tail (L) and right-tail (R) non-coverage error rates, coverage probabilities (CP) and expected widths (EW) of the 95% confidence intervals.

| $\sigma_1 = 1$ | Bonett and Price CI | | | | CI based on $f(\widehat{\theta})$ | | | | Welch CI | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $\sigma_2$ | L | CP | R | EW | L | CP | R | EW | L | CP | R | EW |
| | | | | | $(n_1, n_2) = (5, 5)$; $(\mu_1, \mu_2) = (3, 3)$ | | | | | | | |
| .01 | .033 | .951 | .016 | .807 | .025 | .949 | .025 | .777 | .025 | .949 | .026 | .778 |
| .05 | .034 | .951 | .015 | .806 | .026 | .950 | .024 | .776 | .025 | .949 | .025 | .775 |
| .10 | .034 | .949 | .016 | .807 | .026 | .949 | .026 | .777 | .026 | .949 | .025 | .776 |
| .30 | .034 | .949 | .017 | .804 | .028 | .947 | .025 | .780 | .026 | .947 | .027 | .781 |
| .50 | .029 | .954 | .017 | .836 | .026 | .952 | .022 | .825 | .025 | .950 | .025 | .827 |
| .80 | .022 | .961 | .017 | .962 | .022 | .957 | .021 | 1.00 | .023 | .955 | .022 | 1.04 |
| .90 | .020 | .962 | .018 | 1.02 | .022 | .958 | .021 | 1.09 | .022 | .956 | .022 | 1.19 |
| .95 | .020 | .962 | .018 | 1.05 | .021 | .957 | .022 | 1.23 | .023 | .955 | .023 | 1.28 |
| .99 | .018 | .963 | .019 | 1.09 | .021 | .957 | .023 | 1.39 | .023 | .954 | .023 | 1.43 |
| | | | | | $(n_1, n_2) = (5, 10)$; $(\mu_1, \mu_2) = (3, 3)$ | | | | | | | |
| .01 | .033 | .952 | .016 | .809 | .024 | .950 | .025 | .778 | .025 | .951 | .024 | .780 |
| .05 | .034 | .950 | .016 | .810 | .025 | .950 | .025 | .779 | .025 | .950 | .025 | .778 |
| .10 | .035 | .950 | .016 | .807 | .026 | .949 | .025 | .777 | .026 | .949 | .026 | .777 |
| .30 | .037 | .946 | .017 | .801 | .030 | .945 | .025 | .774 | .026 | .947 | .027 | .772 |
| .50 | .037 | .946 | .017 | .804 | .032 | .944 | .024 | .783 | .028 | .944 | .027 | .779 |
| .80 | .031 | .951 | .018 | .835 | .029 | .948 | .023 | .828 | .027 | .947 | .026 | .826 |
| .90 | .029 | .954 | .018 | .853 | .028 | .950 | .022 | .852 | .026 | .948 | .026 | .852 |
| .95 | .028 | .953 | .018 | .866 | .029 | .949 | .022 | .870 | .025 | .950 | .025 | .868 |
| .99 | .027 | .955 | .019 | .877 | .028 | .950 | .022 | .885 | .026 | .949 | .025 | .886 |
| | | | | | $(n_1, n_2) = (10, 10)$; $(\mu_1, \mu_2) = (3, 3)$ | | | | | | | |
| .01 | .034 | .950 | .016 | .468 | .025 | .950 | .025 | .463 | .025 | .949 | .026 | .464 |
| .05 | .033 | .951 | .016 | .469 | .024 | .950 | .026 | .464 | .025 | .950 | .025 | .464 |
| .10 | .034 | .951 | .015 | .470 | .025 | .950 | .024 | .465 | .025 | .950 | .025 | .465 |
| .30 | .034 | .950 | .016 | .482 | .026 | .949 | .024 | .478 | .026 | .949 | .025 | .477 |
| .50 | .031 | .951 | .017 | .509 | .026 | .949 | .024 | .507 | .026 | .949 | .025 | .507 |
| .80 | .026 | .954 | .020 | .582 | .025 | .951 | .023 | .588 | .024 | .951 | .026 | .590 |
| .90 | .023 | .956 | .020 | .615 | .024 | .952 | .023 | .627 | .024 | .951 | .025 | .630 |
| .95 | .023 | .955 | .022 | .632 | .024 | .951 | .025 | .647 | .024 | .952 | .025 | .652 |
| .99 | .022 | .955 | .023 | .651 | .024 | .951 | .025 | .670 | .025 | .950 | .025 | .676 |
| | | | | | $(n_1, n_2) = (5, 20)$; $(\mu_1, \mu_2) = (3, 3)$ | | | | | | | |
| .01 | .034 | .950 | .015 | .810 | .025 | .950 | .025 | .779 | .024 | .951 | .025 | .779 |
| .05 | .034 | .951 | .015 | .810 | .025 | .950 | .025 | .779 | .025 | .949 | .026 | .776 |
| .10 | .033 | .952 | .015 | .807 | .025 | .950 | .025 | .777 | .025 | .949 | .026 | .778 |
| .30 | .036 | .948 | .016 | .806 | .028 | .948 | .024 | .777 | .027 | .946 | .027 | .771 |
| .50 | .038 | .945 | .017 | .802 | .031 | .944 | .025 | .776 | .026 | .945 | .029 | .769 |
| .80 | .037 | .946 | .018 | .804 | .032 | .944 | .024 | .785 | .029 | .943 | .028 | .780 |
| .90 | .036 | .946 | .017 | .808 | .032 | .945 | .023 | .792 | .027 | .944 | .029 | .787 |
| .95 | .034 | .947 | .019 | .811 | .031 | .945 | .024 | .796 | .029 | .944 | .028 | .792 |
| .99 | .035 | .947 | .018 | .814 | .032 | .944 | .024 | .801 | .029 | .943 | .029 | .797 |
| | | | | | $(n_1, n_2) = (20, 5)$; $(\mu_1, \mu_2) = (3, 3)$ | | | | | | | |
| .01 | .033 | .950 | .017 | .309 | .025 | .950 | .025 | .308 | .025 | .951 | .025 | .308 |
| .05 | .032 | .951 | .018 | .311 | .025 | .950 | .024 | .309 | .025 | .950 | .025 | .309 |
| .10 | .031 | .952 | .016 | .315 | .025 | .950 | .025 | .313 | .025 | .950 | .025 | .314 |
| .30 | .027 | .954 | .019 | .363 | .024 | .952 | .024 | .363 | .024 | .951 | .025 | .365 |
| .50 | .024 | .952 | .024 | .462 | .023 | .950 | .027 | .471 | .026 | .949 | .025 | .479 |
| .80 | .021 | .949 | .030 | .682 | .024 | .946 | .031 | .766 | .027 | .945 | .028 | .813 |
| .90 | .020 | .947 | .033 | .772 | .024 | .945 | .031 | .887 | .027 | .945 | .029 | .949 |
| .95 | .018 | .948 | .034 | .820 | .024 | .944 | .033 | .938 | .028 | .945 | .028 | 1.10 |
| .99 | .018 | .947 | .035 | .872 | .024 | .944 | .032 | 1.11 | .028 | .943 | .030 | 1.26 |
| .01 | .033 | .950 | .017 | .365 | .025 | .950 | .025 | .363 | .024 | .951 | .025 | .363 |
| .05 | .032 | .951 | .017 | .365 | .025 | .950 | .025 | .363 | .025 | .950 | .026 | .363 |
| .10 | .033 | .951 | .017 | .366 | .025 | .950 | .025 | .364 | .024 | .951 | .025 | .364 |
| .30 | .032 | .950 | .018 | .377 | .025 | .949 | .026 | .375 | .025 | .949 | .026 | .375 |
| .50 | .030 | .952 | .019 | .400 | .025 | .950 | .025 | .400 | .026 | .948 | .026 | .399 |
| .80 | .026 | .953 | .022 | .459 | .025 | .951 | .025 | .462 | .025 | .950 | .025 | .462 |
| .90 | .025 | .953 | .022 | .483 | .025 | .950 | .025 | .488 | .026 | .951 | .024 | .490 |
| .95 | .024 | .954 | .022 | .497 | .025 | .951 | .024 | .503 | .025 | .951 | .025 | .504 |
| .99 | .023 | .953 | .023 | .510 | .025 | .950 | .025 | .518 | .025 | .951 | .024 | .520 |

(*continued*).

**Table 3.** Continued.

| $\sigma_1 = 1$ | Bonett and Price CI | | | | CI based on $f(\widehat{\theta})$ | | | | Welch CI | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $\sigma_2$ | L | CP | R | EW | L | CP | R | EW | L | CP | R | EW |
| | | | | | $(n_1, n_2) = (10, 30); (\mu_1, \mu_2) = (3, 3)$ | | | | | | | |
| .01 | .034 | .951 | .016 | .469 | .025 | .951 | .025 | .464 | .025 | .950 | .025 | .464 |
| .05 | .034 | .950 | .016 | .469 | .025 | .950 | .025 | .464 | .025 | .950 | .025 | .464 |
| .10 | .033 | .951 | .016 | .469 | .025 | .951 | .025 | .464 | .025 | .950 | .025 | .463 |
| .30 | .034 | .950 | .016 | .472 | .026 | .949 | .025 | .468 | .026 | .949 | .025 | .466 |
| .50 | .033 | .951 | .016 | .479 | .026 | .950 | .024 | .475 | .026 | .948 | .026 | .475 |
| .80 | .032 | .950 | .018 | .499 | .027 | .948 | .024 | .497 | .026 | .949 | .025 | .497 |
| .90 | .032 | .950 | .018 | .510 | .027 | .948 | .024 | .508 | .025 | .949 | .026 | .506 |
| .95 | .032 | .951 | .018 | .514 | .028 | .948 | .024 | .512 | .026 | .948 | .026 | .512 |
| .99 | .030 | .951 | .019 | .519 | .027 | .948 | .024 | .519 | .025 | .948 | .026 | .518 |
| | | | | | $(n_1, n_2) = (30, 10); (\mu_1, \mu_2) = (3, 3)$ | | | | | | | |
| .01 | .031 | .950 | .018 | .248 | .025 | .950 | .025 | .247 | .025 | .950 | .025 | .247 |
| .05 | .031 | .950 | .019 | .248 | .025 | .950 | .025 | .247 | .026 | .949 | .025 | .247 |
| .10 | .031 | .951 | .018 | .251 | .026 | .950 | .024 | .250 | .026 | .950 | .025 | .250 |
| .30 | .028 | .952 | .020 | .278 | .024 | .950 | .025 | .278 | .024 | .951 | .024 | .278 |
| .50 | .025 | .952 | .022 | .330 | .024 | .951 | .024 | .331 | .025 | .950 | .025 | .333 |
| .80 | .021 | .951 | .027 | .442 | .024 | .949 | .026 | .452 | .025 | .951 | .024 | .456 |
| .90 | .019 | .952 | .028 | .486 | .024 | .950 | .026 | .502 | .025 | .950 | .025 | .507 |
| .95 | .019 | .951 | .030 | .509 | .024 | .949 | .027 | .529 | .025 | .948 | .027 | .533 |
| .99 | .018 | .951 | .031 | .532 | .023 | .949 | .028 | .556 | .026 | .948 | .025 | .564 |
| | | | | | $(n_1, n_2) = (20, 60); (\mu_1, \mu_2) = (3, 3)$ | | | | | | | |
| .01 | .032 | .950 | .017 | .309 | .025 | .950 | .025 | .308 | .025 | .950 | .025 | .308 |
| .05 | .031 | .951 | .017 | .309 | .025 | .951 | .025 | .308 | .025 | .950 | .025 | .308 |
| .10 | .032 | .951 | .018 | .310 | .025 | .950 | .025 | .308 | .026 | .949 | .026 | .308 |
| .30 | .032 | .950 | .018 | .313 | .025 | .950 | .025 | .312 | .026 | .949 | .026 | .312 |
| .50 | .031 | .951 | .018 | .320 | .025 | .949 | .026 | .319 | .025 | .951 | .025 | .318 |
| .80 | .031 | .951 | .019 | .336 | .026 | .950 | .024 | .335 | .025 | .950 | .025 | .335 |
| .90 | .029 | .951 | .019 | .343 | .025 | .951 | .024 | .342 | .026 | .949 | .025 | .342 |
| .95 | .028 | .952 | .020 | .347 | .025 | .950 | .024 | .346 | .024 | .951 | .025 | .347 |
| .99 | .028 | .951 | .020 | .351 | .025 | .950 | .025 | .351 | .026 | .950 | .025 | .351 |
| | | | | | $(n_1, n_2) = (60, 20); (\mu_1, \mu_2) = (3, 3)$ | | | | | | | |
| .01 | .029 | .950 | .020 | .172 | .025 | .950 | .025 | .172 | .025 | .951 | .024 | .172 |
| .05 | .030 | .950 | .021 | .172 | .025 | .949 | .025 | .172 | .025 | .950 | .025 | .172 |
| .10 | .029 | .951 | .020 | .174 | .025 | .950 | .025 | .174 | .025 | .949 | .026 | .174 |
| .30 | .027 | .951 | .021 | .193 | .024 | .951 | .025 | .193 | .024 | .950 | .026 | .193 |
| .50 | .025 | .950 | .024 | .228 | .025 | .949 | .026 | .228 | .025 | .950 | .025 | .228 |
| .80 | .022 | .951 | .027 | .299 | .025 | .950 | .025 | .302 | .026 | .949 | .025 | .303 |
| .90 | .021 | .951 | .028 | .327 | .025 | .949 | .025 | .331 | .024 | .951 | .025 | .332 |
| .95 | .020 | .952 | .028 | .341 | .025 | .951 | .025 | .346 | .026 | .948 | .026 | .347 |
| .99 | .020 | .950 | .030 | .355 | .025 | .949 | .027 | .361 | .025 | .950 | .025 | .362 |
| .01 | .028 | .950 | .022 | .782 | .025 | .950 | .025 | .779 | .025 | .950 | .024 | .778 |
| .05 | .030 | .946 | .024 | .777 | .027 | .946 | .026 | .774 | .026 | .948 | .026 | .775 |
| .10 | .030 | .947 | .024 | .776 | .027 | .946 | .026 | .773 | .027 | .946 | .027 | .775 |
| .30 | .023 | .956 | .022 | .940 | .022 | .955 | .022 | .945 | .023 | .955 | .022 | .948 |
| .50 | .020 | .956 | .024 | 1.29 | .022 | .955 | .023 | 1.33 | .024 | .953 | .023 | 1.35 |
| .80 | .018 | .951 | .031 | 2.01 | .023 | .950 | .027 | 2.31 | .025 | .950 | .025 | 2.43 |
| .90 | .018 | .949 | .033 | 2.30 | .024 | .948 | .028 | 2.92 | .025 | .949 | .026 | 2.78 |
| .95 | .018 | .950 | .033 | 2.44 | .025 | .947 | .028 | 3.10 | .026 | .947 | .027 | 3.18 |
| .99 | .017 | .949 | .034 | 2.60 | .024 | .946 | .030 | 3.47 | .027 | .944 | .029 | 3.69 |
| | | | | | $(n_1, n_2) = (5, 10); (\mu_1, \mu_2) = (9, 3)$ | | | | | | | |
| .01 | .028 | .950 | .022 | .782 | .025 | .950 | .025 | .779 | .026 | .949 | .026 | .778 |
| .05 | .028 | .949 | .023 | .778 | .025 | .949 | .026 | .775 | .026 | .948 | .026 | .775 |
| .10 | .031 | .946 | .023 | .774 | .028 | .946 | .026 | .771 | .029 | .944 | .027 | .771 |
| .30 | .027 | .949 | .024 | .814 | .026 | .949 | .025 | .814 | .025 | .949 | .025 | .812 |
| .50 | .022 | .954 | .024 | .957 | .024 | .953 | .024 | .964 | .023 | .953 | .024 | .966 |
| .80 | .019 | .955 | .027 | 1.29 | .023 | .953 | .023 | 1.33 | .024 | .953 | .024 | 1.33 |
| .90 | .017 | .954 | .028 | 1.43 | .023 | .953 | .024 | 1.48 | .025 | .951 | .024 | 1.49 |
| .95 | .017 | .954 | .029 | 1.49 | .024 | .952 | .024 | 1.56 | .024 | .951 | .025 | 1.57 |
| .99 | .017 | .953 | .030 | 1.57 | .023 | .951 | .025 | 1.65 | .024 | .952 | .024 | 1.66 |

(*continued*).

**Table 3.** Continued.

| $\sigma_1 = 1$ | Bonett and Price CI | | | | CI based on $f(\widehat{\theta})$ | | | | Welch CI | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $\sigma_2$ | L | CP | R | EW | L | CP | R | EW | L | CP | R | EW |
| $(n_1, n_2) = (10, 10); (\mu_1, \mu_2) = (9, 3)$ | | | | | | | | | | | | |
| .01 | .028 | .950 | .022 | .464 | .025 | .950 | .024 | .464 | .025 | .950 | .025 | .464 |
| .05 | .028 | .949 | .022 | .467 | .025 | .950 | .025 | .467 | .025 | .950 | .025 | .467 |
| .10 | .028 | .949 | .023 | .476 | .026 | .949 | .025 | .476 | .025 | .949 | .026 | .475 |
| .30 | .025 | .951 | .024 | .594 | .025 | .951 | .025 | .595 | .025 | .951 | .024 | .596 |
| .50 | .021 | .952 | .027 | .807 | .024 | .951 | .025 | .814 | .024 | .951 | .025 | .816 |
| .80 | .019 | .951 | .030 | 1.20 | .024 | .951 | .025 | 1.24 | .025 | .949 | .026 | 1.24 |
| .90 | .018 | .951 | .032 | 1.34 | .025 | .949 | .026 | 1.40 | .026 | .948 | .025 | 1.41 |
| .95 | .017 | .951 | .032 | 1.42 | .025 | .949 | .026 | 1.49 | .025 | .949 | .026 | 1.50 |
| .99 | .017 | .950 | .033 | 1.50 | .024 | .949 | .027 | 1.58 | .025 | .950 | .024 | 1.59 |
| $(n_1, n_2) = (5, 20); (\mu_1, \mu_2) = (9, 3)$ | | | | | | | | | | | | |
| .01 | .028 | .950 | .022 | .782 | .025 | .950 | .025 | .779 | .025 | .950 | .025 | .777 |
| .05 | .029 | .949 | .023 | .780 | .026 | .949 | .026 | .777 | .025 | .950 | .025 | .776 |
| .10 | .029 | .948 | .023 | .776 | .026 | .947 | .026 | .773 | .026 | .948 | .026 | .773 |
| .30 | .031 | .944 | .025 | .778 | .029 | .944 | .027 | .777 | .029 | .942 | .029 | .774 |
| .50 | .027 | .949 | .024 | .829 | .028 | .948 | .024 | .830 | .027 | .947 | .027 | .830 |
| .80 | .023 | .951 | .026 | .994 | .026 | .950 | .024 | 1.00 | .025 | .951 | .024 | 1.00 |
| .90 | .022 | .952 | .026 | 1.06 | .026 | .951 | .024 | 1.07 | .025 | .951 | .024 | 1.07 |
| .95 | .020 | .953 | .026 | 1.10 | .024 | .952 | .023 | 1.11 | .024 | .952 | .024 | 1.11 |
| .99 | .020 | .953 | .026 | 1.14 | .025 | .952 | .023 | 1.15 | .025 | .951 | .024 | 1.16 |
| $(n_1, n_2) = (20, 5); (\mu_1, \mu_2) = (9, 3)$ | | | | | | | | | | | | |
| .01 | .028 | .950 | .022 | .308 | .026 | .950 | .025 | .308 | .025 | .950 | .025 | .309 |
| .05 | .026 | .951 | .023 | .320 | .024 | .951 | .025 | .320 | .025 | .950 | .025 | .320 |
| .10 | .026 | .950 | .024 | .360 | .024 | .950 | .026 | .360 | .024 | .951 | .025 | .360 |
| .30 | .025 | .945 | .030 | .712 | .026 | .944 | .030 | .720 | .028 | .944 | .028 | .724 |
| .50 | .023 | .944 | .033 | 1.18 | .027 | .943 | .030 | 1.23 | .029 | .943 | .028 | 1.24 |
| .80 | .019 | .946 | .035 | 1.98 | .025 | .946 | .029 | 2.32 | .027 | .945 | .028 | 2.31 |
| .90 | .018 | .947 | .035 | 2.28 | .026 | .945 | .028 | 2.86 | .026 | .945 | .028 | 2.83 |
| .95 | .017 | .947 | .036 | 2.44 | .025 | .945 | .030 | 3.23 | .026 | .947 | .027 | 3.21 |
| .99 | .016 | .948 | .036 | 2.60 | .025 | .944 | .031 | 3.39 | .027 | .942 | .030 | 3.19 |
| .01 | .028 | .950 | .023 | .363 | .025 | .949 | .026 | .363 | .026 | .950 | .025 | .363 |
| .05 | .028 | .950 | .022 | .366 | .025 | .950 | .025 | .366 | .025 | .950 | .025 | .366 |
| .10 | .027 | .950 | .023 | .374 | .025 | .949 | .026 | .374 | .026 | .949 | .025 | .374 |
| .30 | .025 | .949 | .025 | .473 | .025 | .949 | .026 | .473 | .025 | .951 | .024 | .473 |
| .50 | .022 | .952 | .026 | .639 | .024 | .952 | .024 | .642 | .025 | .951 | .024 | .643 |
| .80 | .020 | .950 | .030 | .943 | .025 | .949 | .026 | .959 | .025 | .950 | .026 | .961 |
| .90 | .019 | .950 | .031 | 1.05 | .025 | .949 | .026 | 1.07 | .025 | .950 | .024 | 1.08 |
| .95 | .018 | .951 | .031 | 1.10 | .025 | .950 | .026 | 1.13 | .025 | .950 | .025 | 1.13 |
| .99 | .018 | .950 | .032 | 1.16 | .025 | .949 | .026 | 1.19 | .026 | .950 | .025 | 1.20 |
| $(n_1, n_2) = (10, 30); (\mu_1, \mu_2) = (9, 3)$ | | | | | | | | | | | | |
| .01 | .029 | .949 | .022 | .464 | .026 | .949 | .025 | .464 | .026 | .950 | .025 | .464 |
| .05 | .028 | .950 | .022 | .466 | .025 | .950 | .025 | .465 | .025 | .950 | .024 | .465 |
| .10 | .028 | .949 | .023 | .468 | .025 | .949 | .026 | .467 | .026 | .949 | .025 | .468 |
| .30 | .029 | .948 | .023 | .501 | .027 | .948 | .025 | .501 | .025 | .949 | .025 | .501 |
| .50 | .025 | .951 | .024 | .574 | .026 | .950 | .024 | .575 | .025 | .950 | .025 | .575 |
| .80 | .023 | .951 | .027 | .734 | .025 | .950 | .025 | .738 | .025 | .951 | .024 | .738 |
| .90 | .021 | .952 | .027 | .796 | .025 | .951 | .024 | .803 | .025 | .950 | .025 | .802 |
| .95 | .020 | .951 | .029 | .828 | .024 | .950 | .026 | .835 | .024 | .950 | .026 | .835 |
| .99 | .020 | .951 | .029 | .861 | .025 | .950 | .025 | .870 | .025 | .950 | .025 | .871 |
| $(n_1, n_2) = (30, 10); (\mu_1, \mu_2) = (9, 3)$ | | | | | | | | | | | | |
| .01 | .026 | .951 | .023 | .247 | .024 | .951 | .025 | .247 | .026 | .949 | .025 | .247 |
| .05 | .026 | .951 | .023 | .254 | .025 | .950 | .025 | .254 | .025 | .949 | .026 | .254 |
| .10 | .027 | .950 | .024 | .276 | .025 | .949 | .025 | .276 | .024 | .951 | .025 | .276 |
| .30 | .024 | .949 | .027 | .470 | .025 | .949 | .026 | .472 | .026 | .948 | .026 | .473 |
| .50 | .022 | .949 | .029 | .732 | .026 | .948 | .026 | .741 | .025 | .949 | .025 | .740 |
| .80 | .018 | .950 | .032 | 1.16 | .025 | .949 | .026 | 1.20 | .026 | .948 | .026 | 1.20 |
| .90 | .017 | .950 | .033 | 1.31 | .025 | .950 | .026 | 1.37 | .025 | .949 | .026 | 1.37 |
| .95 | .017 | .950 | .033 | 1.39 | .025 | .949 | .026 | 1.46 | .026 | .950 | .025 | 1.46 |
| .99 | .016 | .951 | .033 | 1.46 | .025 | .950 | .025 | 1.55 | .025 | .949 | .026 | 1.55 |

(*continued*).

**Table 3.** Continued.

| $\sigma_1 = 1$ | Bonett and Price CI | | | | CI based on $f(\widehat{\theta})$ | | | | Welch CI | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $\sigma_2$ | L | CP | R | EW | L | CP | R | EW | L | CP | R | EW |
| | | | | | $(n_1, n_2) = (20, 60); (\mu_1, \mu_2) = (9, 3)$ | | | | | | | |
| .01 | .027 | .950 | .022 | .308 | .025 | .951 | .025 | .308 | .025 | .950 | .025 | .308 |
| .05 | .027 | .950 | .023 | .309 | .025 | .950 | .025 | .309 | .025 | .950 | .025 | .309 |
| .10 | .028 | .949 | .023 | .312 | .026 | .949 | .025 | .311 | .025 | .950 | .025 | .311 |
| .30 | .027 | .950 | .023 | .341 | .025 | .950 | .025 | .341 | .024 | .950 | .025 | .340 |
| .50 | .025 | .951 | .025 | .395 | .024 | .950 | .025 | .395 | .024 | .951 | .024 | .395 |
| .80 | .023 | .951 | .026 | .508 | .025 | .950 | .025 | .510 | .025 | .949 | .025 | .510 |
| .90 | .023 | .949 | .027 | .551 | .026 | .949 | .025 | .553 | .025 | .950 | .024 | .553 |
| .95 | .022 | .951 | .027 | .574 | .024 | .951 | .025 | .576 | .025 | .950 | .025 | .576 |
| .99 | .022 | .951 | .027 | .596 | .025 | .950 | .025 | .599 | .025 | .950 | .025 | .599 |
| | | | | | $(n_1, n_2) = (60, 20); (\mu_1, \mu_2) = (9, 3)$ | | | | | | | |
| .01 | .026 | .950 | .024 | .172 | .025 | .950 | .025 | .172 | .025 | .950 | .025 | .172 |
| .05 | .026 | .949 | .025 | .177 | .024 | .949 | .027 | .177 | .025 | .950 | .025 | .177 |
| .10 | .026 | .950 | .025 | .193 | .025 | .950 | .026 | .193 | .025 | .950 | .025 | .193 |
| .30 | .024 | .950 | .026 | .322 | .025 | .949 | .026 | .322 | .025 | .950 | .025 | .322 |
| .50 | .022 | .950 | .028 | .491 | .025 | .950 | .025 | .494 | .025 | .950 | .025 | .494 |
| .80 | .019 | .951 | .030 | .766 | .025 | .950 | .025 | .777 | .024 | .950 | .026 | .777 |
| .90 | .018 | .950 | .032 | .860 | .024 | .950 | .026 | .875 | .025 | .950 | .025 | .876 |
| .95 | .018 | .949 | .032 | .908 | .025 | .949 | .026 | .926 | .026 | .949 | .025 | .928 |
| .99 | .018 | .949 | .033 | .957 | .024 | .950 | .026 | .978 | .025 | .950 | .025 | .980 |

**Table 4.** Test and reference data.

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Test ($x_1$) | 41.05 | 47.79 | 35.73 | 28.48 | 27.30 | 22.82 | 38.62 |
| | 25.99 | 29.38 | 36.27 | 40.59 | 19.38 | | |
| Ref ($x_2$) | 18.25 | 37.99 | 24.09 | 36.47 | 24.60 | 29.25 | 28.27 |
| | 32.77 | 25.79 | 32.50 | 32.41 | 19.52 | 31.13 | |

**Table 5.** Confidence intervals and $p$-values for testing the ratio of means.

| Methods | 90% CIs | 95% CIs | 99% CIs | $p$-Values for $H_a : \theta \neq 1$ |
|---|---|---|---|---|
| MLRT | (0.966, 1.34) | (0.930, 1.38) | (0.855, 1.48) | 0.1834 |
| Fiducial | (0.959, 1.35) | (0.921, 1.40) | (0.838, 1.52) | 0.2012 |
| Bonett & Price | (0.971, 1.34) | (0.938, 1.39) | (0.873, 1.49) | 0.1757 |
| Approx. CI (15) | (0.966, 1.34) | (0.932, 1.39) | (0.862, 1.49) | 0.1850 |
| Welch | (0.966, 1.34) | (0.930, 1.39) | (0.857, 1.48) | 0.1842 |

MLRT, we computed the MLRT statistic as 1.3304 and the $p$-value as $2[1 - \Phi(1.3304)] = 0.1834$. The results of the Welch method and those based on the MLRT are very similar.

The fiducial CIs are slightly wider than the other CIs and the $p$-value of the fiducial test is a little larger than those of the other tests. These comparisons are in agreement with our simulation results where we noticed that the fiducial approach is somewhat conservative.

## 5. Concluding remarks

The proposed Welch CI and the closed-form CI based on the df $f(\widehat{\theta})$ are simple and easy to compute. On the basis of our numerical studies, we find that Algorithm 1, with the closed-form CI based on the df $f(\widehat{\theta})$ as starting values, always produced bona fide CIs for the ratio of means. Our extensive simulation studies indicate that these two CIs control the coverage probabilities very close to the nominal level with balanced non-coverage tail error rates even for small samples. These two CIs can be safely used in bioassay and bioequivalence studies where the comparison of means is required.

Furthermore, the Welch CI and the closed-form CI based on the df $f(\widehat{\theta})$ are very similar to the CIs based on the MLRT even for some small sample sizes. Even though we encountered some computational issues as noted in Section 3, the inferential results based on the MLRT are known to be very accurate even for small samples; see Wu and Jiang [10] and the references therein.

## Disclosure statement

No potential conflict of interest was reported by the authors.

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