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Research article

Accurate inference for the Youden index and its associated cutoff point based on the gamma and inverse Gaussian distributed assumption

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Abstract: The Youden index is often used to measure the effectiveness of biomarkers and aids to find the optimal cutoff point. Since pooled specimens have been shown to be an effective cost-cutting technique, we proposed the exact inferential procedures for the Youden index and its associated cutoff point based on the pooled specimens under the gamma or the inverse Gaussian assumption. The generalized confidence intervals (GCIs) were proposed for the Youden index and its associated cutoff point. Monte Carlo simulations were used to assess the performance of the proposed GCIs. The simulation results show that the proposed GCIs outperformed existing methods such as the bootstrap-p CIs in terms of the coverage probability. Finally, the proposed procedures were illustrated by an example.

Keywords: Youden index; gamma distribution; inverse Gaussian distribution; generalized pivotal quantity; pooled specimens
Mathematics Subject Classification: 62F30

1. Introduction

The Youden index was first introduced in medical literature by Youden [1]. It is a commonly used index to measure the effectiveness of the overall diagnosis. The Youden index has a wide range of applications in the medicine and biology fields [2–4]. Demir et al. [5] used the Youden index to measure the differentiation between thalamic traits and iron deficiency anemia. Schisterman et al. [6] used the Youden index to analyze a data set related to the coronary calcium score. Otto et al. [7] used the Youden index to diagnose Creutzfeldt-Jakob disease by the measurement of the $S100$ protein in serum. For more examples, one can refer to [8–10].

For any given cutoff point c, sensitivity(c) represents the probability of a diseased individual having a positive test result, and specificity(c) represents the probability of a healthy individual having

a negative test result. Then the Youden index J is defined as

$$\begin{aligned} J &= \max_c \{\text{sensitivity}(c) + \text{specificity}(c) - 1\} \\ &= \text{sensitivity}(c^*) + \text{specificity}(c^*) - 1, \end{aligned}$$

where c^* are the optimal cutoff points of the test results. As described by Perkins and Schisterman [11], the Youden index J is a biomarker's greatest differentiating ability when given the same weight to sensitivity and specificity. The range of J is from 0 to 1, and a value of 0 means that the diagnosis is ineffective, while a value of 1 means that the diagnosis is perfect.

For diagnostic purposes, biomarkers can be divided into patient (cases) and healthy (controls) groups. Let f_1 and f_2 be the probability density functions (PDFs) of the cases and controls, respectively. We know from Schisterman et al. [12] that the optimal cutoff point to separate the cases and controls is the intersection of two density functions, then the optimal cutoff point c^* can be obtained based on the following criterions:

$$f_1(c^*) = f_2(c^*), \tag{1.1}$$

$$f_1(c^* + \varepsilon) > f_2(c^* + \varepsilon), \text{ for some small } \varepsilon > 0. \tag{1.2}$$

The criterion (1.2) is necessary when there exist multiple intersections. This is true when the mean of the cases is greater than the mean of the controls.

Statistical inference on the Youden index has been extensively studied. Nakas et al. [13] used a generalization of the Youden index to analysis cutoff point selection problems in three-class classification, and used nonparametric and parametric approaches to estimate the Youden index and the cutoff points. Fluss et al. [2] compared several estimation procedures for the Youden index and its associated cutoff point. Liu [14] proposed an alternative to the traditional methods based on the Youden index and the closest-to-$(0, 1)$ criterion for threshold selection, and used nonparametric method to search for the optimal cutoff point. Rota and Antolini [15] used theoretical and simulation investigation to compare four methods commonly used to define cutoff points of continuous biomarkers. Nakaset et al. [16] extended the Youden index to k-class classification problems. For more literature on the Youden index, one can refer to [17–21].

However, costs may hinder the evaluation of the effectiveness of new biomarkers. Smaller number of pooled specimens method have been used by analysts in order to cost-cutting, which has been shown to be an effective cost-cutting technique [22–24]. Assume that $X_1, X_2, \ldots, X_N$ are the biomarker values of the case individuals, and $Y_1, Y_2, \ldots, Y_M$ are the biomarker values of the control individuals. As described by Gunasekera et al. [25], the average of the member's measurements can be seen as the pool's measurement. Suppose that there are n and m pooled observations available of cases and controls, respectively, with groups of size g. Then $n = N/g$, and $m = M/g$. Assume that $X_1, X_2, \ldots, X_N$ are randomly placed into the case groups with size g, and $Y_1, Y_2, \ldots, Y_M$ are randomly placed into the control groups with size g. Denote $XP_1, XP_2, \ldots, XP_n$ as the pooled observations for the case groups, and $YP_1, YP_2, \ldots, YP_m$ as the pooled observations for the control groups. Then from Gunasekera et al. [25], we have $XP_j = \frac{1}{g}\sum_{i=1}^{g} X_{i,j}$, $j = 1, 2, \ldots, n$, and $YP_k = \frac{1}{g}\sum_{i=1}^{g} Y_{i,k}$, $k = 1, 2, \ldots, m$, where $X_{i,j}$ is the ith biomarker value in the jth case group, and $Y_{i,k}$ is the ith biomarker value in the kth control group. For more information on the inference for the Youden index and its associated optimal cutoff point based on pooled specimens, one can refer to [12, 25–28].

As everyone knows, the gamma and inverse Gaussian (IG) distributions are two commonly used distributions in statistics. They have a wide range of applications in several fields, including but not limited to reliability theory, life test, financial analysis, biostatistics, health science, ecology, entomology, etc., which should be attributed to their very natural and excellent probabilistic and statistical properties. However, few of the existing studies on the Youden index involve gamma and IG distributions, especially for the latter, which is the original intention and motivation of our research. In this paper, we propose exact inference procedures for the Youden index and its associated cutoff point based on the pooled specimens under the gamma or the IG assumption. According to our experience, the method proposed in this paper has better coverage probabilities (CPs), even when the sample size is small. Our approach is based on the tool of generalized pivotal quantities (GPQs), which was introduced in [29]. For the literatures on constructing confidence intervals for the Youden index and its associated cutoff point based on the GPQ method, one can refer to [25, 30], in which the two-parameter exponential and other distributions were assumed.

The rest of this paper is organized as follows. In Section 2, we provide the inferential method for the Youden index and its associated optimal cutoff point based on the gamma assumption. The GCIs for the Youden index and its associated optimal cutoff point are also derived under the IG distributions in Section 3. In Section 4, we use Monte Carlo simulation to assess the performances of the proposed inference procedures. In Section 5, the proposed procedures are illustrated by an example. Finally, we provide some conclusions in Section 6.

2. Gamma distributed biomarker

Let X and Y denote the results on a specific biomarker for the diseased and healthy subjects, respectively. Suppose that X and Y have independent gamma distributions with $X \sim \text{Gamma}(\alpha_1, \beta_1)$ and $Y \sim \text{Gamma}(\alpha_2, \beta_2)$. The PDF and cumulative distribution function (CDF) of the gamma distribution $\text{Gamma}(\alpha, \beta)$ are given by

$$f_{Ga}(t|\alpha,\beta) = \frac{1}{\Gamma(\alpha)\beta^{\alpha}} t^{\alpha-1} e^{-\frac{t}{\beta}}, t > 0,$$

and

$$F_{Ga}(t|\alpha,\beta) = \int_0^t f_{Ga}(\upsilon|\alpha,\beta)d\upsilon, t > 0.$$

Where α is the shape parameter, β is the scale parameter, and $\Gamma(s) = \int_0^{+\infty} t^{s-1}e^{-t}dt$ is the gamma function. Without loss of generality, we assume that $\alpha_1\beta_1 > \alpha_2\beta_2$. If $\alpha_1\beta_1 < \alpha_2\beta_2$, the following inference can be used by switching the cases with the controls.

As discussed previously, the optimal cutoff point is realized at an intersection of the PDFs of cases and controls. When $\alpha_1 = \alpha_2 = \alpha$, then

$$\begin{aligned} c^* &= c^*(\alpha, \beta_1, \beta_2) \\ &= \alpha \log\left(\frac{\beta_1}{\beta_2}\right)\left(\frac{1}{\beta_2} - \frac{1}{\beta_1}\right)^{-1}. \end{aligned}$$

When $\beta_1 = \beta_2 = \beta$, then

$$\begin{aligned} c^* &= c^*(\alpha_1, \alpha_2, \beta) \\ &= \beta \left(\frac{\Gamma(\alpha_1)}{\Gamma(\alpha_2)} \right)^{\frac{1}{\alpha_1 - \alpha_2}}. \end{aligned}$$

Otherwise, there may exist one or two real solutions to c^*. McCrimmon [31] provided the following solution

$$c^* = c^*(\alpha_1, \alpha_2, \beta_1, \beta_2) = \frac{\mathbf{W}(k\theta)}{k},$$

where $\mathbf{W}(\cdot)$ is the Lambert-W function, and

$$k = \frac{\beta_1 - \beta_2}{(\alpha_1 - \alpha_2)\beta_1\beta_2}, \ \theta = \left(\frac{\Gamma(\alpha_1)\beta_1^{\alpha_1}}{\Gamma(\alpha_2)\beta_2^{\alpha_2}} \right)^{\frac{1}{\alpha_1 - \alpha_2}}.$$

From [31], we know that when $k\theta \geq 0$, $\mathbf{W}(k\theta)$ is single-valued, and otherwise, $\mathbf{W}(k\theta)$ is double-valued. When $k\theta > -e^{-1}$, all values of $\mathbf{W}(k\theta)$ are real. When $\mathbf{W}(k\theta)$ is double-valued, the optimal cutoff point $c^*(\alpha_1, \alpha_2, \beta_1, \beta_2)$ is located based on the criterion (1.2).

After getting the optimal cutoff point c^*, the Youden index J can be expressed as

$$\begin{aligned} J &= J(\alpha_1, \alpha_2, \beta_1, \beta_2, c^*) \\ &= F_{Ga}(c^*|\alpha_2, \beta_2) - F_{Ga}(c^*|\alpha_1, \beta_1). \end{aligned}$$

Let $XP_i, i = 1, 2, \ldots, n$, and $YP_j, j = 1, 2, \ldots, m$, be the pooled observations for cases and controls, respectively. By virtue of the additivity of the gamma distribution, we have

$$XP_i \sim \text{Gamma}(\alpha_{1p}, \beta_{1p}), \ i = 1, 2, \ldots, n,$$

$$YP_j \sim \text{Gamma}(\alpha_{2p}, \beta_{2p}), \ j = 1, 2, \ldots, m,$$

where $\alpha_{1p} = g\alpha_1, \alpha_{2p} = g\alpha_2, \beta_{1p} = \beta_1/g$, and $\beta_{2p} = \beta_2/g$.

2.1. GCIs for the optimal cutoff point c^* and Youden index J

In this subsection, we will derive the GCIs for c^* and J by using the GPQ method. To derive these GCIs, the following lemmas, which are given by Wang and Wu [32], are needed.

Lemma 2.1. *Let $Z_1, Z_2, \cdots, Z_n$ be a random sample of size n from a gamma population Gamma(α, β), $\overline{Z} = \sum_{i=1}^n Z_i/n$, $\widetilde{Z} = \left(\prod_{i=1}^n Z_i\right)^{1/n}$, $T = \log(\widetilde{Z}/\overline{Z})$. Then the ϑth cumulant of the statistic T is*

$$\begin{aligned} \kappa_1(\alpha) &= \log(n) + \psi(\alpha) - \psi(n\alpha), \\ \kappa_\vartheta(\alpha) &= \frac{1}{n^{i-1}}\psi^{(\vartheta-1)}(\alpha) - \psi^{(\vartheta-1)}(n\alpha), \vartheta = 2, 3, \ldots, \end{aligned}$$

where ψ is the digamma function, and $\psi^{(\vartheta)}(\cdot)$ is the ϑth derivative of $\psi(\cdot)$.

Lemma 2.2. *Let $\kappa_\vartheta(\alpha)$ be the ϑth cumulant of the statistic T. Define $Q(\alpha,\tau)$ by*

$$\begin{aligned} Q(\alpha,\tau) = u_\tau &+ \frac{1}{6}\kappa_3'(\alpha)(u_\tau^2-1) + \frac{1}{24}\kappa_4'(\alpha)(u_\tau^3-3u_\tau) - \frac{1}{36}(\kappa_3'(\alpha))^2(2u_\tau^3-5u_\tau) \\ &+ \frac{1}{120}\kappa_5'(\alpha)(u_\tau^4-6u_\tau^2+3) - \frac{1}{24}\kappa_3'(\alpha)\kappa_4'(\alpha)(u_\tau^4-5u_\tau^2+2) \\ &+ \frac{1}{324}(\kappa_3'(\alpha))^3(12u_\tau^4-53u_\tau^2+17), \end{aligned}$$

where $\kappa_i'(\alpha) = \kappa_i(\alpha)/(\kappa_2(\alpha))^{i/2}$, $i = 3,4,5$, and u_τ is the τ percentile of the standard normal distribution. Then, based on the Cornish-Fisher expansion, the τ percentile of the statistic T can be approximated by $\kappa_1(\alpha) + [\kappa_2(\alpha)]^{1/2}Q(\alpha,\tau)$.

Let

$$\overline{X} = \sum_{i=1}^{n} XP_i/n,\ \widetilde{X} = \left(\prod_{i=1}^{n} XP_i\right)^{1/n},\ T_1 = \log(\widetilde{X}/\overline{X}),$$

and

$$\overline{Y} = \sum_{i=1}^{m} YP_i/m,\ \widetilde{Y} = \left(\prod_{i=1}^{m} YP_i\right)^{1/m},\ T_2 = \log(\widetilde{Y}/\overline{Y}).$$

We know from Iliopoulos [33] that the CDFs of the statistics T_1 and T_2 are strictly decreasing functions of α_{1p} and α_{2p}, respectively.

Let $F_{T_1}(t_1|\alpha_{1p})$ and $F_{T_2}(t_2|\alpha_{2p})$ be the CDFs of the statistics T_1 and T_2, respectively. Then $U_1 = F_{T_1}(T_1|\alpha_{1p})$ and $U_2 = F_{T_2}(T_2|\alpha_{2p})$ are independent standard uniform $U(0,1)$ random variables. Hence T_1 and T_2 can be regarded as the U_1 and U_2 quantiles of $F_{T_1}(T_1|\alpha_{1p})$ and $F_{T_2}(T_2|\alpha_{2p})$, respectively. Therefore, for given $U_1 \sim U(0,1)$ and $U_2 \sim U(0,1)$, the following equations can be obtained based on the Cornish-Fisher expansion.

$$T_1 = \kappa_1(\alpha_{1p}) + [\kappa_2(\alpha_{1p})]^{1/2}Q(\alpha_{1p},U_1), \tag{2.1}$$

$$T_2 = \kappa_1(\alpha_{2p}) + [\kappa_2(\alpha_{2p})]^{1/2}Q(\alpha_{2p},U_2). \tag{2.2}$$

Suppose that $h_1(T_1,U_1)$ and $h_2(T_2,U_2)$ represent the solutions of the Eqs (2.1) and (2.2), respectively. Then $\alpha_{1p} = h_1(T_1,U_1)$ and $\alpha_{2p} = h_2(T_2,U_2)$.

Notice that $2n\overline{X}/\beta_{1p} \sim \chi^2(2n\alpha_{1p})$ and $2m\overline{Y}/\beta_{2p} \sim \chi^2(2m\alpha_{2p})$.

Then we have

$$V_1 = 2n\overline{X}/\beta_{1p} \sim \chi^2(2nh_1(T_1,U_1)),$$

and

$$V_2 = 2m\overline{Y}/\beta_{2p} \sim \chi^2(2mh_2(T_2,U_2)).$$

Since $\beta_{1p} = \beta_1/g, \beta_{2p} = \beta_2/\mathrm{g}$. Therefore, the approximate GPQs of the parameters β_1 and β_2 are given by

$$W_1 = 2ng\overline{X}/V_1, \tag{2.3}$$

$$W_2 = 2mg\overline{Y}/V_2, \tag{2.4}$$

respectively.

When $\alpha_1 \neq \alpha_2, \beta_1 \neq \beta_2$, using the substitution method proposed by Weerahandi [29], the GPQ for c^* can be derived by replacing $(\alpha_1, \alpha_2, \beta_1, \beta_2)$ in the expressions of c^* for $(h_1(T_1, U_1)/g, h_2(T_2, U_2)/g, W_1, W_2)$. Hence, the GPQ for c^* is given by

$$W_3 = c^*(h_1(T_1, U_1)/g, h_2(T_2, U_2)/g, W_1, W_2). \tag{2.5}$$

The GPQ for J can be derived by replacing $(\alpha_1, \alpha_2, \beta_1, \beta_2, c^*)$ in the expressions of J for $(h_1(T_1, U_1)/g, h_2(T_2, U_2)/g, W_1, W_2, W_3)$. Hence, the GPQ for J is given by

$$W_4 = J(h_1(T_1, U_1)/g, h_2(T_2, U_2)/g, W_1, W_2, W_3). \tag{2.6}$$

When $\alpha_1 = \alpha_2 = \alpha$, define $T_3 = T_1 + T_2$. Let $F_{T_3}(t_3|\alpha)$ be the CDF of the statistic T_3. Similarly, $U_3 = F_{T_3}(T_3|\alpha)$ is a uniform $U(0, 1)$ random variable. For given U_3, we have

$$T_3 = \kappa_1(\alpha) + [\kappa_2(\alpha)]^{1/2} Q(\alpha, U_3), \tag{2.7}$$

where $\kappa_i(\alpha)$ in the expression (2.7) are

$$\kappa_1(\alpha) = \log(n) + \log(m) + 2\psi(\alpha) - \psi(n\alpha) - \psi(m\alpha),$$
$$\kappa_\vartheta(\alpha) = \frac{1}{n^{i-1}}\psi^{(\vartheta-1)}(\alpha) + \frac{1}{m^{i-1}}\psi^{(\vartheta-1)}(\alpha) - \psi^{(\vartheta-1)}(n\alpha) - \psi^{(\vartheta-1)}(m\alpha), \vartheta = 2, 3, \cdots.$$

Let $h_3(T_3, U_3)$ be the solution of the Eq (2.7), and then $\alpha = h_3(T_3, U_3)$. Using the substitution method, we have the following results:

$$V_1^* = \frac{2n\overline{X}}{\beta_{1p}} \sim \chi^2(2nh_3(T_3, U_3)), V_2^* = \frac{2m\overline{Y}}{\beta_{2p}} \sim \chi^2(2mh_3(T_3, U_3)).$$

Hence the approximate GPQs of the parameters β_1 and β_2 are given by

$$W_1^* = 2ng\overline{X}/V_1^*, \tag{2.8}$$
$$W_2^* = 2mg\overline{Y}/V_2^*. \tag{2.9}$$

Based on the substitution method, the GPQs for c^* and J are given by

$$W_3^* = c^*(h_3(T_3, U_3)/g, h_3(T_3, U_3)/g, W_1^*, W_2^*), \tag{2.10}$$
$$W_4^* = J(h_3(T_3, U_3)/g, h_3(T_3, U_3)/g, W_1^*, W_2^*, W_3^*), \tag{2.11}$$

respectively.

When $\beta_1 = \beta_2 = \beta$, we have

$$V_3 = \frac{2\left(n\overline{X} + m\overline{Y}\right)}{\beta/g} \sim \chi^2\left(2nh_1(T_1, U_1) + 2mh_2(T_2, U_2)\right).$$

Then the approximate GPQs for β, c^*, and J are given by

$$W_1^{**} = g\left(2n\overline{X} + 2m\overline{Y}\right)/V_3, \tag{2.12}$$

$$W_3^{**} = c^*(h_1(T_1, U_1)/g, h_2(T_2, U_2)/g, W_1^{**}, W_1^{**}), \tag{2.13}$$

$$W_4^{**} = J(h_1(T_1, U_1)/g, h_2(T_2, U_2)/g, W_1^{**}, W_1^{**}, W_3^{**}), \tag{2.14}$$

respectively.

Let $W_{i,\tau}$ be the τ quantile of W_i. Then when $\alpha_1 \neq \alpha_2, \beta_1 \neq \beta_2$, $[W_{i,\tau/2}, W_{i,1-\tau/2}], i = 3, 4$ are the $100(1-\tau)\%$ GCIs for c^* and J, respectively. The following Monte Carlo simulation algorithm can be used to obtain the quantiles of W_i.

Algorithm 1 : GCIs for c^* and J based on gamma distribution.

Step 1. For the given data set, compute $\overline{X}, \overline{Y}, T_1$, and T_2.

Step 2. Generate $U_1 \sim U(0, 1), U_2 \sim U(0, 1)$, and then obtain $h_1(T_1, U_1)$, $h_2(T_2, U_2)$ by using the Eqs (2.1) and (2.2), respectively.

Step 3. Generate $V_1 \sim \chi^2(2nh_1(T_1, U_1)), V_2 \sim \chi^2(2mh_2(T_2, U_2))$, use the Eqs (2.3) and (2.4) to compute W_1, W_2.

Step 4. Compute W_3 based on the Eq (2.5). If W_3 is not a real number, then return to step 2. Otherwise, go to step 5.

Step 5. Compute W_4 based on the Eq (2.6).

Step 6. Repeat Steps 2 to 5 B times. Then we can obtain B values of W_i, $i = 3, 4$.

Step 7. Sort all W_i values in order: $W_{i,(1)} < W_{i,(2)} < \cdots < W_{i,(B)}$. Then the τ quantile of W_i can be estimated by $W_{i,(\tau B)}$.

Let $W_{i,\tau}^*$ and $W_{i,\tau}^{**}$ be the τ quantiles of W_i^* and W_i^{**}, respectively. Then when $\alpha_1 = \alpha_2$, the $100(1-\tau)\%$ GCIs for c^* and J are given by $[W_{i,\tau/2}^*, W_{i,1-\tau/2}^*], i = 3, 4$, respectively. When $\beta_1 = \beta_2$, $[W_{i,\tau/2}^{**}, W_{i,1-\tau/2}^{**}], i = 3, 4$ are the $100(1-\tau)\%$ GCIs for c^* and J, respectively. Similar to Algorithm 1, we can get estimates of these quantiles.

2.2. Hypothesis testing

In practice, we are interested in the following hypothesis testings

I. $H_0 : \alpha_1 = \alpha_2$, $H_1 : \alpha_1 \neq \alpha_2$.

II. $H_0 : \beta_1 = \beta_2$, $H_1 : \beta_1 \neq \beta_2$.

We use the generalized p-value procedure to complete the related hypothesis testing problems. The generalized test variables for the hypothesis testing problems I and II are

$$W_5 = h_1(T_1, U_1) - h_2(T_2, U_2) - (\alpha_1 - \alpha_2),$$
$$W_6 = W_1 - W_2 - (\beta_1 - \beta_2),$$

respectively. The generalized p-value for testing the hypothesis problems are given by

$$\begin{aligned} p_1 &= 2\min\{P(W_5 \leq 0|\alpha_1 = \alpha_2), P(W_5 > 0|\alpha_1 = \alpha_2)\}, \\ &= 2\min\{P(h_1(T_1, U_1) \leq h_2(T_2, U_2)), P(h_1(T_1, U_1) > h_2(T_2, U_2))\}, \end{aligned} \tag{2.15}$$

$$\begin{aligned} p_2 &= 2\min\{P(W_6 \leq 0|\beta_1 = \beta_2), P(W_6 > 0|\beta_1 = \beta_2)\}, \\ &= 2\min\{P(W_1 \leq W_2), P(W_1 > W_2)\}, \end{aligned} \tag{2.16}$$

respectively.

The following Monte Carlo algorithm can be used to evaluate the generalized p-value in (2.15) and (2.16).

Algorithm 2 : Generalized p-value procedures for the hypothesis testing.
Step 1. Compute $\overline{X}_1, \overline{X}_2, T_1$, and T_2 based on the observed data set.
Step 2. Generate $U_1 \sim U(0,1), U_2 \sim U(0,1)$, obtain the solutions $h_1(T_1, U_1)$ and $h_2(T_2, U_2)$ based on the Eqs (2.1) and (2.2), respectively.
Step 3. Generate $V_1 \sim \chi^2(2nh_1(T_1, U_1)), V_2 \sim \chi^2(2mh_2(T_2, U_2))$, use the Eqs (2.3) and (2.4) to compute W_1, W_2.
Step 4. Repeat Steps 2 and 3 B times. Then $P(h_1(T_1, U_1) \leq h_2(T_2, U_2))$ and $P(W_1 \leq W_2)$ can be estimated by the proportion of the events $\{h_1(T_1, U_1) \leq h_2(T_2, U_2\}$ and $\{W_1 \leq W_2\}$, respectively.
Step 5. Compute the generalized p-values in the Eqs (2.15) and (2.16).

3. IG distributed biomarker

Suppose that X and Y have independent IG distributions with $X \sim \text{IG}(\mu_1, \lambda_1)$ and $Y \sim \text{IG}(\mu_2, \lambda_2)$. The PDF and CDF of the IG distribution $\text{IG}(\mu, \lambda)$ are given by

$$f_{IG}(x|\lambda, \mu) = \sqrt{\frac{\lambda}{2\pi x^3}} \exp\left\{-\frac{\lambda}{2x}\left(\frac{x}{\mu} - 1\right)^2\right\}, x > 0, \tag{3.1}$$

and

$$F_{IG}(x|\lambda, \mu) = \Phi\left[\sqrt{\frac{\lambda}{x}}\left(\frac{x}{\mu} - 1\right)\right] + \exp(2\lambda/\mu)\Phi\left[-\sqrt{\frac{\lambda}{x}}\left(\frac{x}{\mu} + 1\right)\right], x > 0, \tag{3.2}$$

respectively. Here $\mu > 0$ is the mean parameter, and $\lambda > 0$ is the shape parameter. Also, we assume that $\mu_1 > \mu_2$. If $\mu_1 < \mu_2$, the following inference can be used by switching the cases with controls.

When X and Y have independent IG distributions, based on the criterion (1.1), the intersections of the PDFs of cases and controls are

$$c_{1,2}(\lambda_1, \lambda_2, \mu_1, \mu_2) = \frac{F \pm \sqrt{F^2 - 4EG}}{2E}, \tag{3.3}$$

where $E = \mu_2^2\lambda_1 - \mu_1^2\lambda_2$, $F = 2\mu_1\lambda_1\mu_2^2 - 2\mu_1^2\mu_2\lambda_2 + \mu_1^2\mu_2^2 \log(\lambda_1/\lambda_2)$, and $G = \mu_1^2\mu_2^2(\lambda_2 - \lambda_1)$. The optimal cutoff point $c^*(\lambda_1, \lambda_2, \mu_1, \mu_2)$ is located based on the criterion (1.2).

After getting the optimal cutoff point c^*, the Youden index J can be expressed as

$$\begin{aligned} J &= J(\lambda_1, \lambda_2, \mu_1, \mu_2, c^*) \\ &= F_{IG}(c^*|\lambda_2, \mu_2) - F_{IG}(c^*|\lambda_1, \mu_1). \end{aligned}$$

In order to develop the interval estimation methods, the following lemma is needed. This result is obvious, and can be found in Folks and Chhikara [34].

Lemma 3.1. *For a random sample $X_1, X_2, \cdots, X_n$ from $IG(\mu, \lambda)$, then*

$$\frac{1}{n}\sum_{i=1}^{n} X_i \sim IG(\mu, n\lambda), \lambda \sum_{i=1}^{n}\left(\frac{1}{X_i} - \frac{n}{\sum_{i=1}^{n} X_i}\right) \sim \chi^2(n-1).$$

Let $XP_i, i = 1, 2, \cdots, n$, and $YP_j, j = 1, 2, \cdots, m$, be the pooled observations of cases and controls, respectively. Then from Lemma 3.1, we have

$$XP_i \sim \text{IG}(\mu_{1p}, \lambda_{1p}), i = 1, 2, \cdots, n,$$
$$YP_j \sim \text{IG}(\mu_{2p}, \lambda_{2p}), j = 1, 2, \cdots, m,$$

where $\mu_{1p} = \mu_1, \mu_{2p} = \mu_2$, $\lambda_{1p} = g\lambda_1$, and $\lambda_{2p} = g\lambda_2$.

Let

$$\overline{X} = \frac{1}{n}\sum_{i=1}^{n} XP_i, \overline{Y} = \frac{1}{m}\sum_{i=1}^{m} YP_i, S_1 = \sum_{i=1}^{n}\left(\frac{1}{XP_i} - \frac{1}{\overline{X}}\right), S_2 = \sum_{i=1}^{m}\left(\frac{1}{YP_i} - \frac{1}{\overline{Y}}\right).$$

Based on Lemma 3.1, we know that

$$\overline{X} \sim \text{IG}(\mu_{1p}, n\lambda_{1p}), \overline{Y} \sim \text{IG}(\mu_{2p}, m\lambda_{2p}), \lambda_{1p}S_1 \sim \chi^2(n-1), \lambda_{2p}S_2 \sim \chi^2(m-1).$$

Let $V_4 = \lambda_{1p}S_1 \sim \chi^2(n-1)$, and $V_5 = \lambda_{2p}S_2 \sim \chi^2(m-1)$. Then the GPQs for λ_1 and λ_2 are

$$W_7 = V_4/(gS_1), \tag{3.4}$$
$$W_8 = V_5/(gS_2). \tag{3.5}$$

Let $U_4 \sim N(0,1), U_5 \sim N(0,1)$, from [35], the approximate GPQs of μ_1 and μ_2 are

$$W_9 = \frac{\overline{X}}{\left|1 + U_4\sqrt{\overline{X}/(nW_7)}\right|}, \tag{3.6}$$
$$W_{10} = \frac{\overline{Y}}{\left|1 + U_5\sqrt{\overline{Y}/(mW_8)}\right|}, \tag{3.7}$$

respectively.

Based on the substitution method, the GPQs of c^* and J are obtained by replacing $(\lambda_1, \lambda_2, \mu_1, \mu_2)$ in c^* and J by (W_7, W_8, W_9, W_{10}). Thus, the GPQs of c^* and J are given by

$$W_{11} = c^*(W_7, W_8, W_9, W_{10}), \tag{3.8}$$
$$W_{12} = J(W_7, W_8, W_9, W_{10}, W_{11}). \tag{3.9}$$

Let $W_{i,\tau}$ be the τ quantile of W_i. Then $[W_{i,\tau/2}, W_{i,1-\tau/2}], i = 11, 12$ are the $100(1-\tau)\%$ GCIs for c^* and J, respectively. The following Monte Carlo simulation algorithm can be used to obtain the quantiles of W_i.

Algorithm 3 : GCIs for c^* and J based on IG distribution.

Step 1. Compute $\overline{X}, \overline{Y}, S_1$, and S_2 based on the observed data set.

Step 2. Generate $U_4 \sim U(0,1), U_5 \sim U(0,1), V_4 \sim \chi^2(n-1)$, and $V_5 \sim \chi^2(m-1)$, compute W_7–W_{10} based on the Eqs (3.4)–(3.7), respectively.

Step 3. Compute W_{11} based on the Eq (3.8). If W_{11} is not a real number, then return to Step 2. Otherwise, go to Step 4.

Step 4. Use the Eq (3.9) to compute W_{12}.

Step 5. Repeat the Steps 2 to 4 B times. Then we can obtain B values of $W_i, i = 11, 12$.
Step 6. Sort all W_i values in order: $W_{i,(1)} < W_{i,(2)} < \cdots < W_{i,(B)}$. Then the τ quantile of W_i can be estimated by $W_{i,(\tau B)}$.

As is known to all, the parametric bootstrap method is a classic approach to obtain confidence intervals for model parameters and some interested quantities. In order to fully evaluate the performances of the proposed GCIs, we also consider the bootstrap-p CIs for the optimal cutoff point c^* and Youden index J based on the IG distribution. The bootstrap-p CIs for the optimal cutoff point c^* and Youden index J based on the gamma distribution can similarly discussed.

In fact, given

$$XP_i \sim \text{IG}(\mu_{1p}, \lambda_{1p}), i = 1, 2, \cdots, n,$$
$$YP_j \sim \text{IG}(\mu_{2p}, \lambda_{2p}), j = 1, 2, \cdots, m,$$

and $\mu_{1p} = \mu_1, \mu_{2p} = \mu_2$, $\lambda_{1p} = g\lambda_1$, and $\lambda_{2p} = g\lambda_2$.

Note that

$$\overline{X} = \frac{1}{n}\sum_{i=1}^{n} XP_i, \overline{Y} = \frac{1}{m}\sum_{i=1}^{m} YP_i, S_1 = \sum_{i=1}^{n}\left(\frac{1}{XP_i} - \frac{1}{\overline{X}}\right), S_2 = \sum_{i=1}^{m}\left(\frac{1}{YP_i} - \frac{1}{\overline{Y}}\right).$$

The maximum likelihood estimates (MLEs) of model parameters $\mu_{1p}, \lambda_{1p}, \mu_{2p}$, and λ_{2p} can be obtained by

$$\widehat{\mu}_{1p} = \overline{X}, \widehat{\lambda}_{1p} = \frac{n}{S_1}, \widehat{\mu}_{2p} = \overline{Y}, \widehat{\lambda}_{2p} = \frac{m}{S_2}.$$

Using the invariance of the MLE, the MLEs of μ_1, λ_1, μ_2, and λ_2 are given as

$$\widehat{\mu}_1 = \widehat{\mu}_{1p} = \overline{X}, \widehat{\lambda}_1 = \frac{n}{gS_1}, \widehat{\mu}_2 = \widehat{\mu}_{2p} = \overline{Y}, \widehat{\lambda}_2 = \frac{m}{gS_2}.$$

On the basis of the model parameters' MLEs $\widehat{\mu}_1, \widehat{\lambda}_1, \widehat{\mu}_2$, and $\widehat{\lambda}_2$, the bootstrap-p CIs for c^* and J based on IG distribution are obtained by the following Algorithm 4.

Algorithm 4 : Bootstrap-p CIs for c^* and J based on IG distribution.
Step 1. Based on the observed data sets $\{XP_i, i = 1, \ldots, n\}$ and $\{YP_j, j = 1, \ldots, m\}$, compute $\overline{X}, \overline{Y}, S_1$, and S_2, get the MLEs of model parameters $\widehat{\mu}_1, \widehat{\mu}_2, \widehat{\lambda}_1$, and $\widehat{\lambda}_2$.
Step 2. Generate the bootstrap samples $\{X^*P_i, i = 1, \ldots, n\}$ and $\{Y^*P_j, j = 1, \ldots, m\}$ from the IG distributions IG$(\widehat{\mu}_1, g\widehat{\lambda}_1)$ and IG$(\widehat{\mu}_2, g\widehat{\lambda}_2)$, compute the bootstrap quantities $\overline{X}^*, \overline{Y}^*, S_1^*$, and S_2^*.
Step 3. Generate random numbers $U_4 \sim U(0, 1), U_5 \sim U(0, 1), V_4 \sim \chi^2(n-1)$, and $V_5 \sim \chi^2(m-1)$, compute the bootstrap GPQs $W_7^* - W_{10}^*$ based on the Eqs (3.4)–(3.7), respectively. ($W_7^* = V_4/(gS_1^*)$, $W_8^* = V_5/(gS_2^*)$).
Step 4. Compute the bootstrap GPQ W_{11}^* based on the Eq (3.8). If W_{11}^* is not a real number, then return to step 3. Otherwise, go to step 5. ($W_{11}^* = c^*(W_7^*, W_8^*, W_9^*, W_{10}^*)$).
Step 5. Use the Eq (3.9) to compute the bootstrap GPQ W_{12}^*.
($W_{12}^* = J(W_7^*, W_8^*, W_9^*, W_{10}^*, W_{11}^*)$).
Step 6. Repeat the Steps 2 to 5 B times. Then we can obtain B values of $W_i^*, i = 11, 12$.
Step 7. Sort all W_i^* values in ascending order: $W_{i,(1)}^* < W_{i,(2)}^* < \cdots < W_{i,(B)}^*$. Then the τ quantile of W_i^* can be estimated by $W_{i,(\tau B)}^*$.

Then the $100(1-\tau)\%$ bootstrap-p CIs for c^* and J are given by $[W_{11,(B\frac{\tau}{2})}^*, W_{11,(B-B\frac{\tau}{2})}^*]$ and $[W_{12,(B\frac{\tau}{2})}^*, W_{12,(B-B\frac{\tau}{2})}^*]$.

4. Simulation study

In this section, the performances of the proposed GCIs for c^* and J are assessed by Monte Carlo simulations. When the biomarker follows the gamma distribution, controls are gamma distributed with parameters $\alpha_2 = 0.5, \beta_2 = 1$, and cases are gamma distributed with $\alpha_1 = 1.5$ and $\beta_1 = 0.5, 1.5, 2$. When the biomarker follows IG distribution, controls are IG distributed with parameters $\mu_2 = 0.3, \lambda_2 = 2$, and cases are IG distributed with $\mu_1 = 0.5$ and $\lambda_1 = 1, 2, 3.5$. In the simulations, we assume that $M = N$. All the simulation results are based on $10,000$ replications with $B = 10,000$.

When the biomarker follows gamma distribution, the CPs and the average lengths (ALs) of the proposed GCIs for c^* and J are listed in Table 1. When the biomarker follows IG distribution, the CPs and the ALs of the proposed GCIs and bootstrap-p CIs for c^* and J are listed in Tables 2–4. It can be seen from Table 1 to Table 4 that the CPs of the proposed GCIs are very close to the nominal levels in all settings. In Tables 2–4, we also compare the GCIs with the bootstrap-p CIs. The results show that the CPs of the bootstrap-p CIs are not close to the nominal levels, especially when the sample size is small. These findings show that the performances of the proposed GCIs are better than bootstrap-p CIs in terms of CP. In addition, from Table 1 to Table 4 we also find that the ALs of the GCIs decrease as the groups of size g increases. This indicates that the pooled specimens method is effective. For fixed parameters β_1 or λ_1, when the total sample size N increases, the ALs of the GCIs become shorter for both gamma and IG distributions as expected. Therefore, we recommend the proposed GCIs for the Youden index J and its associated cutoff point c^* based on gamma and IG distributions.

Note that when the biomarker follows gamma distribution, we do not compare the GCIs with the bootstrap-p CIs because the simulation results are similar to those in the IG case.

Table 1. The CPs and the ALs (in parentheses) of the GCIs for c^* and J with nominal levels 0.90, 0.95, based on 10,000 replications. (gamma case).

(β_1, N)	Parameters	$g = 1$		$g = 2$		$g = 4$	
		0.90	0.95	0.90	0.95	0.90	0.95
(0.5, 30)	c^*	0.9051	0.9544	0.9037	0.9536	0.9059	0.9563
	ALs	(0.2379)	(0.3013)	(0.2230)	(0.2866)	(0.2191)	(0.2832)
	J	0.9003	0.9485	0.9072	0.9531	0.9028	0.9510
	ALs	(0.2845)	(0.3376)	(0.2559)	(0.3046)	(0.2416)	(0.2878)
(0.5, 50)	c^*	0.8995	0.9507	0.9030	0.9508	0.8982	0.9497
	ALs	(0.1688)	(0.2057)	(0.1484)	(0.1824)	(0.1403)	(0.1741)
	J	0.8960	0.9460	0.9037	0.9514	0.8995	0.9523
	ALs	(0.2228)	(0.2649)	(0.1999)	(0.2382)	(0.1889)	(0.2252)
(1.5, 30)	c^*	0.9064	0.9547	0.9122	0.9604	0.9059	0.9602
	ALs	(0.4235)	(0.5153)	(0.3641)	(0.4442)	(0.3383)	(0.4157)
	J	0.9047	0.9523	0.9016	0.9506	0.9025	0.9520
	ALs	(0.2711)	(0.3253)	(0.2272)	(0.2746)	(0.2023)	(0.2464)
(1.5, 50)	c^*	0.9019	0.9492	0.9045	0.9518	0.9035	0.9548
	ALs	(0.3209)	(0.3856)	(0.2755)	(0.3308)	(0.2559)	(0.3071)
	J	0.9019	0.9526	0.9030	0.9528	0.9047	0.9537
	ALs	(0.2113)	(0.2518)	(0.1759)	(0.2100)	(0.1560)	(0.1864)
(2, 30)	c^*	0.9000	0.9515	0.9089	0.9592	0.9109	0.9625
	ALs	(0.4845)	(0.5889)	(0.4028)	(0.4946)	(0.3585)	(0.4440)
	J	0.9100	0.9565	0.9035	0.9507	0.9033	0.9522
	ALs	(0.2580)	(0.3116)	(0.2185)	(0.2672)	(0.1962)	(0.2413)
(2, 50)	c^*	0.8974	0.9503	0.9007	0.9528	0.9084	0.9540
	ALs	(0.3673)	(0.4407)	(0.3038)	(0.3647)	(0.2705)	(0.3262)
	J	0.9003	0.9512	0.9049	0.9557	0.9014	0.9500
	ALs	(0.2007)	(0.2393)	(0.1688)	(0.2016)	(0.1508)	(0.1809)

Table 2. The CPs and the ALs (in parentheses) of the GCIs and bootstrap-p CIs for c^* and J with nominal levels 0.90, 0.95, based on 10,000 replications. (IG case, $g = 1$).

(λ_1, N)	Parameters	GCIs		bootstrap-p CIs	
		0.90	0.95	0.90	0.95
$(1, 20)$	c^*	0.9020	0.9525	0.8525	0.9116
	ALs	(0.1877)	(0.2448)	(0.1581)	(0.2022)
	J	0.9047	0.9543	0.8698	0.9232
	ALs	(0.3337)	(0.3943)	(0.3537)	(0.4214)
$(1, 40)$	c^*	0.8986	0.9517	0.8714	0.9295
	ALs	(0.1160)	(0.1421)	(0.1061)	(0.1283)
	J	0.9011	0.9507	0.8854	0.9401
	ALs	(0.2417)	(0.2869)	(0.2493)	(0.2975)
$(2, 20)$	c^*	0.9082	0.9527	0.8888	0.9389
	ALs	(0.1286)	(0.1616)	(0.1093)	(0.1350)
	J	0.9071	0.9520	0.8545	0.9111
	ALs	(0.3534)	(0.4181)	(0.3640)	(0.4326)
$(2, 40)$	c^*	0.9092	0.9537	0.8997	0.9479
	ALs	(0.0837)	(0.1017)	(0.0768)	(0.0926)
	J	0.9024	0.9494	0.8772	0.9305
	ALs	(0.2567)	(0.3050)	(0.2609)	(0.3107)
$(3.5, 20)$	c^*	0.9077	0.9509	0.8753	0.9311
	ALs	(0.0935)	(0.1146)	(0.0857)	(0.1035)
	J	0.9080	0.9548	0.8569	0.9151
	ALs	(0.3400)	(0.4030)	(0.3463)	(0.4117)
$(3.5, 40)$	c^*	0.9029	0.9512	0.8841	0.9381
	ALs	(0.0625)	(0.0752)	(0.0599)	(0.0717)
	J	0.9016	0.9509	0.8742	0.9298
	ALs	(0.2446)	(0.2908)	(0.2475)	(0.2948)

Table 3. The CPs and the ALs (in parentheses) of the GCIs and bootstrap-p CIs for c^* and J with nominal levels 0.90, 0.95, based on 10,000 replications. (IG case, $g = 2$).

(λ_1, N)	Parameters	GCIs		bootstrap-p CIs	
		0.90	0.95	0.90	0.95
$(1, 20)$	c^*	0.8958	0.9509	0.8389	0.8994
	ALs	(0.1383)	(0.1717)	(0.1136)	(0.1377)
	J	0.9057	0.9535	0.8537	0.9104
	ALs	(0.2597)	(0.3080)	(0.2764)	(0.3305)
$(1, 40)$	c^*	0.9017	0.9514	0.8676	0.9265
	ALs	(0.0901)	(0.1093)	(0.0817)	(0.0981)
	J	0.9008	0.9503	0.8737	0.9289
	ALs	(0.1852)	(0.2202)	(0.1913)	(0.2286)
$(2, 20)$	c^*	0.9063	0.9542	0.8917	0.9437
	ALs	(0.1001)	(0.1231)	(0.0817)	(0.0986)
	J	0.9069	0.9530	0.8379	0.8983
	ALs	(0.2789)	(0.3308)	(0.2884)	(0.3434)
$(2, 40)$	c^*	0.9062	0.9544	0.8977	0.9486
	ALs	(0.0676)	(0.0819)	(0.0606)	(0.0727)
	J	0.9004	0.9497	0.8645	0.9234
	ALs	(0.2000)	(0.2378)	(0.2037)	(0.2427)
$(3.5, 20)$	c^*	0.9084	0.9560	0.8911	0.9419
	ALs	(0.0706)	(0.0865)	(0.0604)	(0.0726)
	J	0.9038	0.9524	0.8259	0.8902
	ALs	(0.2768)	(0.3290)	(0.2795)	(0.3323)
$(3.5, 40)$	c^*	0.9008	0.9494	0.8900	0.9419
	ALs	(0.0476)	(0.0575)	(0.0438)	(0.0525)
	J	0.8982	0.9481	0.8596	0.9177
	ALs	(0.1981)	(0.2357)	(0.1993)	(0.2373)

Table 4. The CPs and the ALs (in parentheses) of the GCIs and bootstrap-p CIs for c^* and J with nominal levels 0.90, 0.95, based on 10,000 replications. (IG case, $g = 4$).

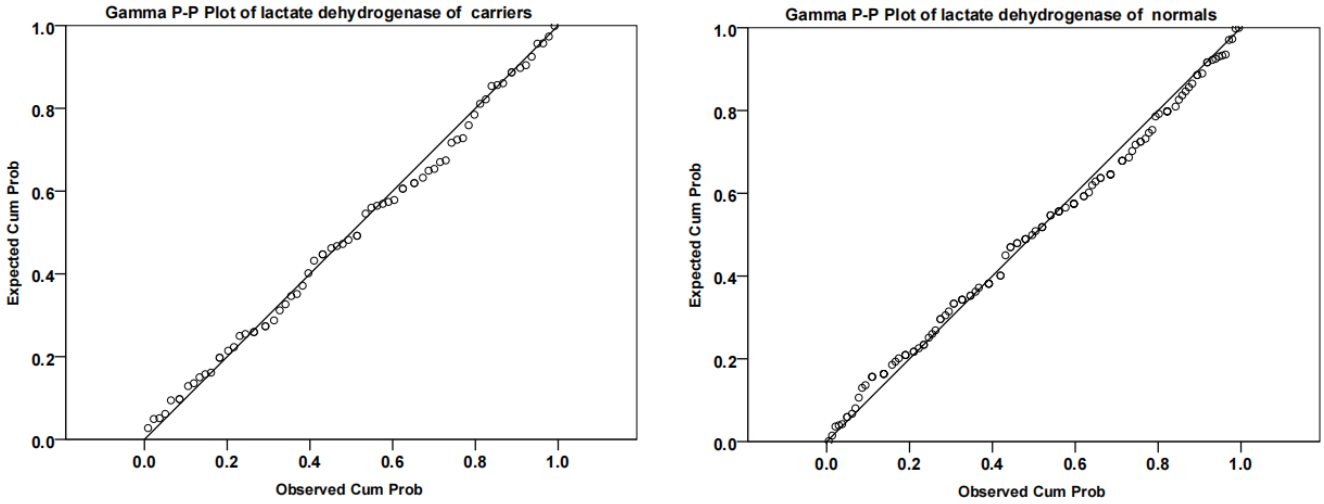
(λ_1, N)	Parameters	GCIs		bootstrap-p CIs	
		0.90	0.95	0.90	0.95
$(1, 20)$	c^*	0.8999	0.9511	0.8228	0.8903
	ALs	(0.1150)	(0.1419)	(0.0921)	(0.1108)
	J	0.9046	0.9552	0.8274	0.8886
	ALs	(0.2097)	(0.2491)	(0.2245)	(0.2687)
$(1, 40)$	c^*	0.9002	0.9489	0.8639	0.9203
	ALs	(0.0771)	(0.0936)	(0.0691)	(0.0828)
	J	0.9031	0.9530	0.8636	0.9232
	ALs	(0.1480)	(0.1761)	(0.1535)	(0.1834)
$(2, 20)$	c^*	0.9078	0.9570	0.9007	0.9505
	ALs	(0.0853)	(0.1050)	(0.0664)	(0.0798)
	J	0.9097	0.9538	0.8129	0.8756
	ALs	(0.2304)	(0.2735)	(0.2396)	(0.2853)
$(2, 40)$	c^*	0.9002	0.9542	0.8961	0.9504
	ALs	(0.0588)	(0.0713)	(0.0512)	(0.0613)
	J	0.9022	0.9512	0.8582	0.9162
	ALs	(0.1639)	(0.1949)	(0.1675)	(0.1996)
$(3.5, 20)$	c^*	0.9089	0.9561	0.8726	0.9226
	ALs	(0.0598)	(0.0736)	(0.0486)	(0.0584)
	J	0.9020	0.9495	0.8049	0.8705
	ALs	(0.2323)	(0.2763)	(0.2353)	(0.2800)
$(3.5, 40)$	c^*	0.9035	0.9531	0.8851	0.9352
	ALs	(0.0404)	(0.0490)	(0.0361)	(0.0432)
	J	0.9075	0.9495	0.8551	0.9151
	ALs	(0.1652)	(0.1967)	(0.1666)	(0.1983)

5. An illustrative example

In this section, the Duchenne Muscular Dystrophy (DMD) data set available at http://lib.stat.cmu.edu/datasets/ is used to illustrate the proposed methods. This data set includes blood samples from carriers and normals, and measures four different variables (creatine kinase (ck), hemopexin (h), pyruvate kinase (pk), and lactate dehydrogenase (ld)). We randomly select carriers and normals of the fourth biomarker in this data set for illustrative purposes. Figures 1(a) and (b) show the gamma P-P plots for those data.

It can be seen from Figure 1 that the gamma distribution can be used to fit those data. Based on the DMD data set, the estimate of the generalized p-value (2.15) is 0.0270, and the estimate of the generalized p-value (2.16) is close to zero. So we reject the null hypothesises in I and II. For $g = 1$, the 90% and 95% GCIs for c^* are given by $(199.5595, 218.7058)$, and $(197.8356, 220.9915)$,

respectively. The 90% and 95% GCIs for J are given by $(0.4145, 0.6009)$, and $(0.3943, 0.6169)$, respectively. For $g = 2$, the 90% and 95% GCIs for c^* are given by $(199.5082, 218.8851)$, and $(197.7328, 221.2453)$, respectively. The 90% and 95% GCIs for J are given by $(0.4133, 0.6023)$, and $(0.3953, 0.6201)$, respectively. For $g = 4$, the 90% and 95% GCIs for c^* are given by $(200.3053, 219.9091)$, and $(198.7090, 222.7552)$, respectively. The 90% and 95% GCIs for J are given by $(0.4295, 0.6493)$, and $(0.4106, 0.6676)$, respectively. We can see that the difference of these intervals is small. This indicates that the pooled specimens method is effective.



(a) (b)

Figure 1. (a) The Gamma P-P plot for lactate dehydrogenase data of the carriers, and (b) the Gamma P-P plot for lactate dehydrogenase data of the normals.

6. Conclusions

In this paper, we proposed the interval estimation methods for the Youden index and its corresponding optimal cutoff point based on the pooled samples under the gamma or IG assumption. Our method is based on the GPQ approach. In the case of the gamma assumption, the GCIs for the Youden index and optimal cutoff points are obtained under equal shape parameters, equal scale parameters, and unequal shape and scale parameters. The generalized p-value procedure is proposed to test whether the shape parameters or the scale parameters are equal. When the biomarker follows the IG distribution, the optimal cutoff point is derived based on the the criterions (1.1) and (1.2). The GCIs are also proposed for the Youden index and its corresponding optimal cutoff point. The Monte Carlo simulation study demonstrated that our methods given in this paper can work well. A real example is given to illustrate the proposed method.

Author contributions

Xiaofei Wang: Conceptualization, Methodology, Validation, Formal analysis, Writing-original draft; Peihua Jiang: Supervision, Methodology, Simulation, Writing-review & editing; Wenzhen Liu:

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Conflict of interest

The authors declare that they have no conflicts of interest.

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