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Confidence interval construction for sensitivity difference of two continuous-scale diagnostic tests at the fixed level of two specificities

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ABSTRACT

We propose five confidence intervals for sensitivity difference of two continuous-scale diagnostic tests at the fixed level of two specificities based on the generalized pivotal quantity method, the hybrid method and the Bootstrap resampling method.

1. Introduction

In comparison study of two diagnostic tests for paired designs, one of the goal is to show that a new diagnostic test is noninferiority to (or better than) the current diagnostic test in terms of their diagnostic accuracies, which can be measured by their corresponding sensitivities and specificities. In these studies, the difference between sensitivities of two diagnostic tests at the fixed level of two specificities is often used as a measure for comparison of their diagnostic accuracies. Comparison of two diagnostic accuracies can be conducted by using CI for the difference of two sensitivities. CI construction of sensitivity difference between two diagnostic tests in a binary paired design has been extensively investigated in the literature. For example, see May and Johnson (1997), Newcombe (1998), Tango (1998) and Tang et al. (2005). Various CIs for the sensitivity difference between two continuous-scale diagnostic tests at the fixed level of two specificities were constructed in past years. For example, see Greenhouse and Mantel (1950) and Linnet (1987) and Wieand et al. (1989) for the nonparametric method, and Qin et al. (2006) for the bootstrap resampling method, and Tian (2013) for the generalized variable method. However, these methods may be sensitive to distributional assumption or the selection of the smoothing parameters in density or computationally intensive for moderate to large sample sizes, and it is impossible to obtain the explicit formulas. Hence, the aim of this paper is to develop a computationally feasible and closed-form CI for the sensitivity difference of two continuous-scale diagnostic tests at the fixed level of two specificities.

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A potential CI for implementing our purpose is the square-and-add interval, which was first proposed by Newcombe (1998) for constructing CI of the difference between two independent proportions and further studied by Donner and Zou (2002), who referred to it as the method of variance estimates recovery (MOVER). Because this method has the closed-form property and performs satisfactory in terms of coverage probability and interval width, it has received a lot of attention over years. For example, see Zou and Donner (2008), Zou et al. (2009), Tang et al. (2010a), Tang et al. (2010b) and Donner and Zou (2002). However, to our knowledge, there is little work done for CI construction of the sensitivity difference between two continuous-scale diagnostic tests at the fixed level of two specificities via the square-and-add method.

To compare our developed CIs with the existing other CIs, we may consider a generalized CI (GCI) via the generalized pivotal quantity (Weerahandi, 1993), which has received considerable attention in recent years because it has been shown to be a useful tool for making inferences in many practical problems (e.g., see Chang and Huang, 2000; Hanning et al., 2006 and Schaarschmidt, 2013). Inspired by Schaarschmidt (2013), this paper proposes a GCI for the sensitivity difference between two continuous-scale diagnostic tests at the fixed level of two specificities, and presents an algorithm to evaluate the proposed GCI.

The paper is organized as follows. A GCI of the sensitivity difference between two continuous-scale diagnostic tests at the fixed level of two specificities is proposed in Section 2. In Section 3, two hybrid CIs are constructed on the basis of the square-and-add method by incorporating the 'Wilson score' method and 'Agresti–Coull' method. Also, two bootstrap CIs are presented in Section 3. Section 4 presents simulation studies to investigate the finite performance of the proposed CIs. A real example is used to illustrate our proposed CIs in Section 5. A brief conclusion is given in Section 6.

2. GCI for sensitivity difference

In this section, the generalized pivotal quantity (GPQ) approach (Weerahandi, 1993) is employed to construct GCI of the sensitivity difference between two continuous-scale diagnostic tests at the fixed level of two specificities.

For $t = 1$ (i.e., diagnostic test T_1) and 2 (i.e., diagnostic test T_2), let X_t and Y_t be outcomes of the tth continuous-scale diagnostic test for a non-diseased and a diseased individual under a paired design, respectively. For a given cut-off point γ_t, sensitivity and specificity of the tth diagnostic test can be defined as

$$\theta_t = P(Y_t \geq \gamma_t) = 1 - F_t(\gamma_t), \qquad \phi_t = P(X_t < \gamma_t) = G_t(\gamma_t),$$

respectively, where F_t and G_t are distribution functions of Y_t and X_t, respectively. Under the assumption that the specificity of the tth diagnostic test is fixed at the level τ_t, the corresponding sensitivity of the tth diagnostic test can be expressed as $\theta_t = 1 - F_t(G_t^{-1}(\tau_t))$, where G_t^{-1} is the inverse function of G_t for $t = 1$ and 2. Thus, the sensitivity difference of two continuous-scale diagnostic tests at the fixed level of specificities ($\tau_1 = \tau_2 = \tau$) is defined as $\theta = \theta_2 - \theta_1 = F_1(G_1^{-1}(\tau)) - F_2(G_2^{-1}(\tau))$. Our main interest is to construct CI of θ. To this end, we assume that $X_{t1}, \ldots, X_{tm_t}$ are the tth diagnostic test outcomes of a random sample from the non-diseased individuals, and $Y_{t1}, \ldots, Y_{tn_t}$ are the tth diagnostic test outcomes of a random sample from the diseased individuals for $t = 1$ and 2.

Suppose that F_t is a normal distribution with mean μ_{st} and variance σ_{st}^2, and G_t is a normal distribution with mean μ_{pt} and variance σ_{pt}^2 for $t = 1$ and 2. Then, we have

$$\theta = \Phi\left(\frac{\mu_{p1} - \mu_{s1} + \sigma_{p1}\Phi^{-1}(\tau)}{\sigma_{s1}}\right) - \Phi\left(\frac{\mu_{p2} - \mu_{s2} + \sigma_{p2}\Phi^{-1}(\tau)}{\sigma_{s2}}\right), \tag{1}$$

where $\Phi(\cdot)$ denotes the cumulative distribution function of the standard normal random variable. Denote $\bar{X}_t = m_t^{-1}\sum_{j=1}^{m_t} X_{tj}$, $\bar{Y}_t = n_t^{-1}\sum_{j=1}^{n_t} Y_{tj}$, $S_{pt}^2 = (m_t - 1)^{-1}\sum_{j=1}^{m_t}(X_{tj} - \bar{X}_t)^2$ and $S_{st}^2 = (n_t - 1)^{-1}\sum_{j=1}^{n_t}(Y_{tj} - \bar{Y}_t)^2$, and let $\bar{x}_t, \bar{y}_t, s_{pt}^2$ and s_{st}^2 denote their corresponding observed values for $t = 1$ and 2. Thus, $\theta = \theta_2 - \theta_1$ can be estimated by

$$\hat{\theta} = \Phi\left(\frac{\bar{x}_1 - \bar{y}_1 + s_{p1}\Phi^{-1}(\tau)}{s_{s1}}\right) - \Phi\left(\frac{\bar{x}_2 - \bar{y}_2 + s_{p2}\Phi^{-1}(\tau)}{s_{s2}}\right).$$

Let $V_{pt} = (m_t - 1)S_{pt}^2/\sigma_{pt}^2$ and $V_{st} = (n_t - 1)S_{st}^2/\sigma_{st}^2$ for $t = 1$ and 2. It can be shown that $V_{pt} \sim \chi_{m_t-1}^2$ and $V_{st} \sim \chi_{n_t-1}^2$. Thus, the generalized pivotal quantities for σ_{pt}^2 and σ_{st}^2 can be expressed as

$$P_{\sigma_{pt}^2} = \frac{(m_t - 1)s_{pt}^2}{V_{pt}} \sim \frac{(m_t - 1)s_{pt}^2}{\chi_{m_t-1}^2}, \qquad P_{\sigma_{st}^2} = \frac{(n_t - 1)s_{st}^2}{V_{st}} \sim \frac{(n_t - 1)s_{st}^2}{\chi_{n_t-1}^2}$$

for $t = 1$ and 2, respectively, where χ_m^2 denotes the chi-squared distribution with m degrees of freedom. Again, $T_{pt} = \sqrt{m_t}(\bar{X}_t - \mu_{pt})/\sigma_{pt}$ and $T_{st} = \sqrt{n_t}(\bar{Y}_t - \mu_{st})/\sigma_{st}$ follow the standard normal distribution. Then, the generalized pivotal quantities for μ_{pt} and μ_{st} can be written as $P_{\mu_{pt}} = \bar{x}_t - T_{pt}\sqrt{P_{\sigma_{pt}^2}/m_t}$ and $P_{\mu_{st}} = \bar{y}_t - T_{st}\sqrt{P_{\sigma_{st}^2}/n_t}$ for $t = 1$ and 2, respectively.

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