Supplementary Material

Comparison of paired ROC curves through a two-stage test

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In this supplement, we present proofs of theorems in the main paper.

1 Proof of Theorem 2.2

Proof. Without loss of generality, assume both markers are standardized in a way that scores of non-diseased subjects follow $N(0, 1)$. That is, $\mu_X = \mu_{\bar{X}} = 0$ and $\sigma_X = \sigma_{\bar{X}} = 1$. Then by Equations (2.4) and (2.5),

$$AUC_1 = \Phi\left(\frac{\mu_Y}{\sqrt{1 + \sigma_Y^2}}\right), \quad AUC_2 = \Phi\left(\frac{\mu_{\bar{Y}}}{\sqrt{1 + \sigma_{\bar{Y}}^2}}\right), \quad (1.1)$$

$$sAUC_1 = \Phi\left(\frac{\mu_Y - c}{\sqrt{1 + \sigma_Y^2}}\right), \quad \text{and}, \quad (1.2)$$

$$sAUC_2 = \Phi\left(\frac{\mu_{\bar{Y}} - c}{\sqrt{1 + \sigma_{\bar{Y}}^2}}\right). \quad (1.3)$$

If declaration (a) follows, since Φ is a cdf and therefore an increasing function, we have

$$\frac{\mu_Y}{\sqrt{1 + \sigma_Y^2}} = \frac{\mu_{\bar{Y}}}{\sqrt{1 + \sigma_{\bar{Y}}^2}} \quad (1.4)$$

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and

$$\frac{1}{\sqrt{1 + \sigma_Y^2}} = \frac{1}{\sqrt{1 + \sigma_{\tilde{Y}}^2}}. \quad (1.5)$$

Immediately, we have $\sigma_Y = \sigma_{\tilde{Y}}$ and $\mu_Y = \mu_{\tilde{Y}}$, thus, the two markers are distributed in the same way and thus declaration (b) follows.

On the other hand, if declaration (b) follows,

$$ROC_1(t) = \Phi\left(\frac{\mu_Y + \Phi^{-1}(t)}{\sigma_Y}\right) \quad \text{and} \quad ROC_2(t) = \Phi\left(\frac{\mu_{\tilde{Y}} + \Phi^{-1}(t)}{\sigma_{\tilde{Y}}}\right)$$

for any $t \in [0, 1]$. This holds if and only if $\sigma_Y = \sigma_{\tilde{Y}}$ and $\mu_Y = \mu_{\tilde{Y}}$. Thus, the two markers have the same distributions and declaration (a) follows. $\square$

2 Proof of Theorem 2.3

Before proving the theorems 2.3 and 2.4, we give the definition of generalized U-statistics, which can be found in many literatures, for example, Lehmann (1963) and Sen (1974). Let $X_1, \dots, X_{n_1}; Y_1, \dots, Y_{n_2}; \dots$ be independent samples of size n_i from distributions F, G , and so on. A generalized-U statistic is defined as

$$U = \binom{n_1}{m_1}^{(-1)} \binom{n_2}{m_2}^{(-1)} \cdots \sum \psi(X_{\alpha_1}, \dots, X_{\alpha_{m_1}}; Y_{\beta_1}, \dots, Y_{\beta_{m_2}}; \dots), \quad (2.1)$$

where the summation extends over all possible sets of subscripts satisfying $1 \leq X_{\alpha_1} < X_{\alpha_2} < \dots < X_{\alpha_{m_1}} \leq n_1$; $1 \leq Y_{\beta_1} < Y_{\beta_2} < \dots < Y_{\beta_{m_2}} \leq n_2$; $\dots$, and $\psi(x_1, \dots, x_{m_1}; y_1, \dots, y_{m_2}; \dots)$ is a function symmetric in the x's, in the y's, and so on. Here, symmetric in the x's means that the function ψ retains the same value at any two permutations of $x_{\alpha_1}, \dots, x_{\alpha_{m_1}}$.

Proof. We rewrite $\widehat{AUC}_1 - \widehat{AUC}_2$ and $s\widehat{AUC}_1 - s\widehat{AUC}_2$ as follows;

$$\begin{aligned} \widehat{AUC}_1 - \widehat{AUC}_2 &= \frac{1}{n_1 n_2} \sum_{i=1}^{n_1} \sum_{j=1}^{n_2} \psi(Y_i, X_j) - \frac{1}{n_3 n_4} \sum_{k=1}^{n_3} \sum_{l=1}^{n_4} \psi(\tilde{Y}_k, \tilde{X}_l) \\ &= \frac{1}{n_1 n_2 n_3 n_4} \sum_{i=1}^{n_1} \sum_{j=1}^{n_2} \sum_{k=1}^{n_3} \sum_{l=1}^{n_4} \varphi^{(1)}(Y_i; X_j; \tilde{Y}_k; \tilde{X}_l) \end{aligned} \quad (2.2)$$

and

$$\begin{aligned} s\widehat{AUC}_1 - s\widehat{AUC}_2 &= \frac{\sum_{i=1}^{n_1} \sum_{j=1}^{n_2} \psi(Y_i, X_j + \hat{\delta})}{n_1 n_2} - \frac{\sum_{k=1}^{n_3} \sum_{l=1}^{n_4} \psi(\tilde{Y}_k, \tilde{X}_l + \hat{\delta})}{n_3 n_4} \\ &= \frac{1}{n_1 n_2 n_3 n_4} \sum_{i=1}^{n_1} \sum_{j=1}^{n_2} \sum_{k=1}^{n_3} \sum_{l=1}^{n_4} \varphi^{(2)}(Y_i; X_j; \tilde{Y}_k; \tilde{X}_l). \end{aligned} \quad (2.3)$$

Then, $\widehat{AUC}_1 - \widehat{AUC}_2$ and $s\widehat{AUC}_1 - s\widehat{AUC}_2$ are two special generalized-U statistics with $m_i = 1$, $i = 1, \dots, 4$. We also note that

$$E(\widehat{AUC}_1 - \widehat{AUC}_2) = AUC_1 - AUC_2$$

and

$$E(s\widehat{AUC}_1 - s\widehat{AUC}_2) = sAUC_1 - sAUC_2,$$

where the expectation is taken with respect to the distribution function $F, G, \tilde{F}$, and $\tilde{G}$. From the result of Lehmann (1963) (Appendix (ii)) about generalized-U statistics, $N^{1/2}(\widehat{AUC}_1 - \widehat{AUC}_2 - (AUC_1 - AUC_2))$ and $N^{1/2}(s\widehat{AUC}_1 - s\widehat{AUC}_2 - (sAUC_1 - sAUC_2))$ are asymptotically bivariate normal with mean zero and covariance matrix $\Sigma = (\sigma_{rs})$ where

$$\sigma_{rs} = (N/n_1)\xi_{1000}^{rs} + (N/n_2)\xi_{0100}^{rs} + (N/n_3)\xi_{0010}^{rs} + (N/n_4)\xi_{0001}^{rs}.$$

ξ_{1000}^{rs} , ξ_{0100}^{rs} , ξ_{0010}^{rs} , and ξ_{0001}^{rs} are covariances between $\varphi^{(r)}(Y_i; X_j; \tilde{Y}_k; \tilde{X}_l)$ and $\varphi^{(s)}(Y_{i'}; X_{j'}; \tilde{Y}_{k'}; \tilde{X}_{l'})$, $\varphi^{(r)}(Y_i; X_j; \tilde{Y}_k; \tilde{X}_l)$ and $\varphi^{(s)}(Y_{i'}; X_j; \tilde{Y}_{k'}; \tilde{X}_{l'})$, $\varphi^{(r)}(Y_i; X_j; \tilde{Y}_k; \tilde{X}_l)$ and $\varphi^{(s)}(Y_{i'}; X_{j'}; \tilde{Y}_k; \tilde{X}_{l'})$, and $\varphi^{(r)}(Y_i; X_j; \tilde{Y}_k; \tilde{X}_l)$ and $\varphi^{(s)}(Y_{i'}; X_{j'}; \tilde{Y}_{k'}; \tilde{X}_l)$, respectively for $i \neq i'$, $j \neq j'$, $k \neq k'$, and $l \neq l'$ for $r, s = 1, 2$. $\square$

3 Proof of Theorem 2.4

Proof. Rewrite $\widehat{AUC}_1 - \widehat{AUC}_2$ and $s\widehat{AUC}_1 - s\widehat{AUC}_2$ as follows;

$$\begin{aligned} \widehat{AUC}_1 - \widehat{AUC}_2 &= \frac{1}{nm} \sum_{i=1}^n \sum_{j=1}^m \psi(Y_i, X_j) - \frac{1}{nm} \sum_{i=1}^n \sum_{j=1}^m \psi(\tilde{Y}_i, \tilde{X}_j) \\ &= \frac{1}{nm} \sum_{i=1}^n \sum_{j=1}^m \varphi^{(1)}(W_i; V_j) \end{aligned} \quad (3.1)$$

and

$$\begin{aligned} s\widehat{AUC}_1 - s\widehat{AUC}_2 &= \frac{1}{nm} [\sum_{i=1}^n \sum_{j=1}^m \psi(Y_i, X_j + \hat{\delta}) - \sum_{i=1}^n \sum_{j=1}^m \psi(\tilde{Y}_i, \tilde{X}_j + \hat{\delta})] \\ &= \frac{1}{nm} \sum_{i=1}^n \sum_{j=1}^m \varphi^{(2)}(W_i; V_j). \end{aligned} \quad (3.2)$$

Since $\{W_i = (Y_i, \tilde{Y}_i)\}$ and $\{V_j = (X_j, \tilde{X}_j)\}$ are independently generated from distributions F and G , $\widehat{AUC}_1 - \widehat{AUC}_2$ and $s\widehat{AUC}_1 - s\widehat{AUC}_2$ are two special generalized-U statistics with $m_i = 1$, $i = 1, 2$, $n_1 = n$ and $n_2 = m$. We also note that

$$E(\widehat{AUC}_1 - \widehat{AUC}_2) = AUC_1 - AUC_2$$

and

$$E(\widehat{sAUC}_1 - \widehat{sAUC}_2) = sAUC_1 - sAUC_2,$$

where the expectation is taken with respect to distribution functions F and G . From the result of Lehmann (1963) (Appendix (ii)) about generalized-U statistics, $N^{1/2}(\widehat{AUC}_1 - \widehat{AUC}_2 - (AUC_1 - AUC_2))$ and $N^{1/2}(\widehat{sAUC}_1 - \widehat{sAUC}_2 - (sAUC_1 - sAUC_2))$ are asymptotically bivariate normal with mean zero and covariance matrix $\Sigma = (\sigma_{rs})$ where $\sigma_{rs} = (N/n)\xi_{10}^{rs} + (N/m)\xi_{01}^{rs}$. Here ξ_{10}^{rs} , ξ_{01}^{rs} are covariances between $\varphi^{(r)}(W_i; V_j)$ and $\varphi^{(s)}(W_i; V_{j'})$, $\varphi^{(r)}(W_i; V_j)$ and $\varphi^{(s)}(W_{i'}; V_j)$, respectively for $i \neq i'$ and $j \neq j'$ for $r, s = 1, 2$. $\square$

References

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