Weight optimization for comparing correlated areas under ROC curve in longitudinal setting

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ABSTRACT

Receiver Operating Characteristic (ROC) curves are often used to evaluate the prognostic performance of a biomarker which might be used to supplement or replace standard clinical examinations. In a previous study, a non-parametric ROC approach was introduced to compare two biomarkers with repeated measurements. An asymptotically normal statistic, which contains the subject-specific weights, was developed to estimate the areas under the ROC curve of biomarkers. Although two weighting schemes were suggested to be optimal when the within-subject correlation is 1 or 0 by the previous study, the universal optimal weight was not determined. We modify this asymptotical statistic to compare AUCs between two correlated groups and propose a solution to weight optimization in non-parametric AUCs comparison to improve the efficiency of the estimator. It is demonstrated how the Lagrange multiplier can be used as a strategy for finding the weights which minimize the variance function subject to constraints. We show substantial gains of efficiency by using the novel weighting scheme when the correlation within subject is high, the correlation between groups is high, and/or the disease incidence is small, which is the case for many longitudinal matched case control studies. An illustrative example is presented to apply the proposed methodology to a thyroid function dataset. Simulation results suggest that the optimal weight performs well with a sample size as small as 50 per group.

KEY WORDS:Receiver Operating Characteristic (ROC); biomarker evaluation; repeated measurements; weight optimization; the Lagrange multiplier; correlated groups; asymptotic relative efficiency (ARE).

1 Introduction

In many clinical trials, the correlated-groups designs are preferred by researchers due to increased statistical power. There are two ways of introducing the correlation among participants in correlated-groups designs: (1) by having a single group of participants exposed to all of the conditions (repeated measures designs); and(2) by matching participants on some important variable(s)(matched-subjects designs). In a matched-subjects design study that has the biomarker with the repeated measurements, it may be of clinical interest to compare the diagnostic/prognostic performance of the biomarker between correlated groups to

determine if the diagnostic/prognostic accuracy in one of the groups is superior. Under these circumstances, the statistics for comparing the biomarkers need to deal with not only within-subject but also between-group correlations.

For evaluating a repeated biomarker in a single group, Emir et al. (1998) proposed a non-parametric estimate of sensitivity and specificity. In 2000, Emir et al. further extended the earlier research and derived the estimation of AUC under the ROC curve for a repeated biomarker. An asymptotic normal statistic was developed to test area under the ROC curve of a repeated biomarker in a single group and the bootstrap method was used to obtain the variance of this estimate. The approach allows for estimating AUC in the presence of within-subject (repeated) correlation. It involves estimating subject-specific sensitivities and specificities and taking weighted averages of these estimates over all subjects.

The nonparametric estimate of AUC proposed by Emir et al. (2000) involves assigning a weight to each subject. Two weighting schemes were suggested: (1) assigning equal weights to all biomarker measurements, and (2) assigning equal weights to all subjects. It was suggested that weighting scheme 1 would be optimal when the correlation within subject is 1 and that weighting scheme 2 would be optimal when the correlation within subject is 0. However, the universal optimal weights were not determined. More recently, a novel solution to the weight optimization problem was introduced by Wu et al. (2011), who proposed the Lagrange Multiplier Method to find the optimal weights, which minimize the variance of AUC estimate for a single repeated biomarker or comparing AUCs from two biomarkers in a single group. The optimal weights for AUC comparison proposed by Wu et al. (2011) dealt with the difference of paired biomarkers from the same subject. To compare AUCs of a repeated biomarker between two correlated groups, we may apply Wu et al.'s method (2011) to each group and obtain two sets of weights, one for each group. However, these weights would not be optimal because the method cannot take the between-group correlation into consideration as the disease progression may be different, and the number of biomarker measurements may be different between groups. A generalization of interest for us is to find the universal optimal weights for comparing AUCs of a repeated biomarker between two correlated groups. The goals of this article are to modify the asymptotic statistics by Emir et al. (2000) to compare AUCs between two correlated groups and obtain the variance of this estimate; to determine the optimal weight sets which can minimize the variance of this estimate; to demonstrate the asymptotic relative efficiency of the optimal weighting scheme; and to show how the between-group correlation, the within-subject correlation, and the incidence rate of disease impact the efficiency.

2 Non-parametric comparison of two correlated AUCs

2.1 Notations

Suppose that we have a random sample of n subjects who were exposed to some existing conditions (the exposed group). Each subject in the exposed group was mathced to a subject who was not exposed to the conditions, based on some confounding variables, such as age or gender. The n subjects resulting from the matching form the non-exposed group. All subjects are being followed for the outcome of disease progression. A biomarker was repeatly measured over time until the end of study or the disease progression. Let X_{ijl} be the continuous random variable whose observations are the biomarker values obtained from the ith group ($i = 1$ if exposed group and $i = 2$ if non-exposed group), for the jth subject ($j = 1, 2, \cdots, n$), at the lth non-progression visit ($l = 1, 2, \cdots, m_{ij}$), where m_{ij} is the

number of non-progression visits for subject j in group i. Let Y_{ij} be the continuous random variable associated with values for the same biomarker from the jth subject in the ith group at the progression visit. Also let $\delta_{ij} = 1$ if subject j in the ith group became a progressor and $= 0$ otherwise. Define $D_i = \sum_{j=1}^{n} \delta_{ij}$ as the total number of progressors in the ith group. Let F_i and G_i be the distribution functions of X_{ijl} and Y_{ij}, respectively. Further, let θ_i represent area under the respective ROC curves of biomarker in the ith group. In this article, we discuss test for the null hypothesis of $H_0 : \theta_1 - \theta_2 = 0$ versus the alternative hypothesis $H_1 : \theta_1 - \theta_2 \neq 0$.

2.2 Non-parametric estimate of area under the ROC

Assume that the biomarker will be considered to be positive if the value of X_{ijl} or Y_{ij} exceeds a predetermined thredhold c. Non-parametric estimate of area under the ROC curve for the biomarker can be obtained using standard method based on the empirical cumulative distribution functions (CDFs) corresponding to F_i and G_i. Area under the ROC curve of a repeated biomarker for the ith group is $\theta_i = \int_{-\infty}^{\infty} F_i(c) dG_i(c)$. The corresponding area estimate, $\hat{\theta}_i$, is given by

$$\hat{\theta}_i = \int_{-\infty}^{\infty} \hat{F}_i(c) d\hat{G}_i(c), \tag{2.1}$$

where

$$\begin{aligned} \hat{F}_i(c) &= \sum_{j=1}^{n} w_{ij} \left\{ \frac{1}{m_{ij}} \sum_{l=1}^{m_{ij}} \mathrm{I}(x_{ijl} \leq c) \right\}, \\ \hat{G}_i(c) &= \frac{1}{D_i} \sum_{j=1}^{n} \delta_{ij} \mathrm{I}(y_{ij} \leq c), \end{aligned}$$

and $(w_{i1}, \cdots, w_{in})$ is a set of weights assigned to subjects in the ith group, satisfying $w_{ij} > 0, j = 1, \cdots, n$ and $\sum_{j=1}^{n} w_{ij} = 1$.
Let $\Delta = \theta_1 - \theta_2$ be the true AUC difference between two correlated groups. The non-parametric estimate of Δ is $\hat{\Delta} = \hat{\theta}_1 - \hat{\theta}_2$, given by

$$\hat{\Delta} = \int_{-\infty}^{\infty} \hat{F}_1(c) d\hat{G}_1(c) - \int_{-\infty}^{\infty} \hat{F}_2(c) d\hat{G}_2(c). \tag{2.2}$$

In next section, we will consider the optimal weights to minimize the variance of $\hat{\Delta}$.

3 The optimal weighting scheme

The estimate of $\hat{\Delta}$ involves a set of weights in each group. We can use two simple weighting schemes that were provided in Emir et al. (2000): (1) assigning equal weights to all biomarker observations in each group, i.e., $w_{ij} = m_{ij} / \sum_{j'=1}^{n} m_{ij'}$, when the within-subject correlation is low; or (2) assigning equal weights to all subjects in each group, i.e., $w_{ij} = 1/n$ when the within-subject correlation is high. Alternatively, we may use the Lagrange Multiplier Method to derive the optimal weights which can minimize the variance of $\hat{\Delta}$.

To derive the optimal weights, we utilize the following fact

$$\hat{\Delta} - \Delta = \sum_{j=1}^{n} (\epsilon_{1j} + \xi_{1j} - \epsilon_{2j} - \xi_{2j}) + o(n^{-1/2}), \tag{3.1}$$

where

$$\begin{aligned} \epsilon_{ij} &= \frac{\delta_{ij}}{D_i} \int_{-\infty}^{\infty} F_i(c) d\left\{ I(y_{ij} \le c) - G_i(c) \right\}, \\ \xi_{ij} &= \frac{w_{ij}}{m_{ij}} \sum_{l=1}^{m_{ij}} \int_{-\infty}^{\infty} \left\{ I(x_{ijl} \le c) - F_i(c) \right\} dG_i(c). \end{aligned}$$

The proof of (3.1) above can be found in Appendix of publication by Emir et. al (2000). Defining the transformations

$$U_{ijl} = G_i(x_{ijl}), \qquad V_{ij} = F_i(y_{ij}), \tag{3.2}$$

we can express the variances of $\hat{\theta}_1$ and $\hat{\theta}_2$, and the covariance between $\hat{\theta}_1$ and $\hat{\theta}_2$ in terms of U_{ijl} and V_{ij}. They are

$$\begin{aligned} Var \sum_{j=1}^{n} (\epsilon_{1j} + \xi_{1j}) &= \sigma_{u1}^2 \sum_{j=1}^{n} \frac{\sum_{l \neq l'} corr(U_{1jl}, U_{1jl'})}{m_{1j}^2} w_{1j}^2 \\ &\quad - \frac{2\sigma_{u1}\sigma_{v1}}{D_1} \sum_{j=1}^{n} \frac{w_{1j}\delta_{1j}}{m_{1j}} \sum_{l=1}^{m_{1j}} corr(U_{1jl}, V_{1j}) + \frac{\sigma_{v1}^2}{D_1}, \\ Var \sum_{j=1}^{n} (\epsilon_{2j} + \xi_{2j}) &= \sigma_{u2}^2 \sum_{j=1}^{n} \frac{\sum_{l \neq l'} corr(U_{2jl}, U_{2jl'})}{m_{2j}^2} w_{2j}^2 \\ &\quad - \frac{2\sigma_{u2}\sigma_{v2}}{D_2} \sum_{j=1}^{n} \frac{w_{2j}\delta_{2j}}{m_{2j}} \sum_{l=1}^{m_{2j}} corr(U_{2jl}, V_{2j}) + \frac{\sigma_{v2}^2}{D_2}, \\ Cov(\sum_{j=1}^{n} (\epsilon_{1j} + \xi_{1j}), \sum_{j=1}^{n} (\epsilon_{2j} + \xi_{2j})) &= \sigma_{u_1}\sigma_{u_2} \sum_{j=1}^{n} \sum_{j=1}^{n} \frac{w_{1j} w_{2j} corr(U_{1jl}, U_{2jl})}{m_{1j} m_{2j}} \\ &\quad + \frac{\sigma_{u_2}\sigma_{v_1}}{D_1} \sum_{j=1}^{n} \frac{w_{2j}\delta_{1j}}{m_{2j}} \sum_{l=1}^{m_{2j}} corr(U_{2jl}, V_{1j}) \\ &\quad + \frac{\sigma_{u_1}\sigma_{v_2}}{D_2} \sum_{j=1}^{n} \frac{w_{1j}\delta_{2j}}{m_{1j}} \sum_{l=1}^{m_{1j}} corr(U_{1jl}, V_{2j}) \\ &\quad + \frac{\sigma_{v_1}\sigma_{v_2} \sum_{j=1}^{n} \delta_{1j} \sum_{j=1}^{n} \delta_{2j} corr(V_{1j}, V_{2j})}{D_1 D_2}, \end{aligned}$$

where $\sigma_{u1}^2 = Var(U_{1jl})$, $\sigma_{v1}^2 = Var(V_{1j})$, $\sigma_{u2}^2 = Var(U_{2jl})$, and $\sigma_{v2}^2 = Var(V_{2j})$.

Thus, the variance of $\hat{\Delta}$ given m_{ij} can be expressed as

$$\begin{aligned} Var(\hat{\Delta}|m_{ij}) &= \mathrm{Var}\sum_{j=1}^{n}(\epsilon_{1j}-\epsilon_{2j}+\xi_{1j}-\xi_{2j}) \\ &= Var\sum_{j=1}^{n}(\epsilon_{1j}+\xi_{1j})+Var\sum_{j=1}^{n}(\epsilon_{2j}+\xi_{2j})-2Cov(\sum_{j=1}^{n}(\epsilon_{1j}+\xi_{1j}),\sum_{j=1}^{n}(\epsilon_{2j}+\xi_{2j})) \\ &= \sum_{j=1}^{n}a_{1j}w_{1j}^2-2\sum_{j=1}^{n}b_{1j}w_{1j}+\sum_{j=1}^{n}a_{2j}w_{2j}^2-2\sum_{j=1}^{n}b_{2j}w_{2j}-2\sum_{j=1}^{n}c_jw_{1j}w_{2j}+d, \end{aligned} \tag{3.3}$$

where

$$\begin{aligned} a_{1j} &= \frac{\sum_{l,l'=1}^{m_{1j}}\sigma_{ll'}^{u_1u_1}}{m_{1j}^2}, \\ a_{2j} &= \frac{\sum_{l,l'=1}^{m_{2j}}\sigma_{ll'}^{u_2u_2}}{m_{2j}^2}, \\ b_{1j} &= \frac{\delta_{1j}\sum_{l=1}^{m_{1j}}\sigma_l^{u_1v_1}}{D_1m_{1j}}-\frac{\delta_{2j}\sum_{l=1}^{m_{1j}}\sigma_l^{u_1v_2}}{D_2m_{1j}}, \\ b_{2j} &= \frac{\delta_{2j}\sum_{l=1}^{m_{2j}}\sigma_l^{u_2v_2}}{D_2m_{2j}}-\frac{\delta_{1j}\sum_{l=1}^{m_{2j}}\sigma_l^{u_2v_1}}{D_1m_{2j}}, \\ c_j &= \frac{\sum_{k}^{m_{1j}}\sum_{l}^{m_{2j}}\sigma_{kl}^{u_1u_2}}{m_{1j}m_{2j}}, \\ d &= \frac{\sigma^{v_1v_1}}{D_1}+\frac{\sigma^{v_2v_2}}{D_2}-2\frac{\sigma^{v_1v_2}}{D_1D_2}, \end{aligned}$$

with $\sigma_{ll'}^{u_iu_i}=Cov(U_{ijl},U_{ijl'})$, $\sigma_l^{u_iv_i}=Cov(U_{ijl},V_{ij})$ and $\sigma^{v_iv_i}=Cov(V_{ij},V_{ij})$.
The method of Lagrange Multiplier provides a strategy for finding the maxima or minima of a function subject to constraints. By applying the Lagrange Multiplier Method in this case, the optimal weights can be obtained to minimize the variance function (3.3) with constraints $w_{1j}>0$, $w_{2j}>0$, $(j=1,\cdots,n)$, $\sum_{j=1}^{n}w_{1j}=1$ and $\sum_{j=1}^{n}w_{2j}=1$. The Lagrange function is defined as

$$L(w_{11},\cdots,w_{1n};w_{21},\cdots,w_{2n};\lambda;\mu)=Var(\hat{\Delta}|m_{ij})+\lambda(1-\sum_{j=1}^{n}w_{1j})+\mu(1-\sum_{j=1}^{n}w_{2j}),$$

where λ and μ are the two Lagrange multipliers.
The partial derivatives of the Lagrange function with respect to w_{1j} and w_{2j} are

$$\begin{cases} \frac{\mathrm{d}L(w_{11},\cdots,w_{1n};w_{21},\cdots,w_{2n};\lambda;\mu)}{\mathrm{d}w_{1j}}=2a_{1j}w_{1j}-2b_{1j}-2c_jw_{2j}-\lambda=0; \\ \frac{\mathrm{d}L(w_{11},\cdots,w_{1n};w_{21},\cdots,w_{2n};\lambda;\mu)}{\mathrm{d}w_{2j}}=2a_{2j}w_{2j}-2b_{2j}-2c_jw_{1j}-\mu=0. \end{cases} \tag{3.4}$$

Let

$$H_j=\begin{pmatrix} a_{1j} & -c_j \\ -c_j & a_{2j} \end{pmatrix}, \quad \widetilde{w_j}=\begin{pmatrix} w_{1j} \\ w_{2j} \end{pmatrix}, \quad \widetilde{b_j}=\begin{pmatrix} b_{1j} \\ b_{2j} \end{pmatrix},$$

and

$$\widetilde{\chi}=\begin{pmatrix} \lambda \\ \mu \end{pmatrix},$$

the system equations (3.4) can be expressed in a matrix format. That is

$$2H_j\widetilde{w_j} - \widetilde{\chi} - 2\widetilde{b_j} = 0.$$

We obtain:

$$\widetilde{w_j} = \frac{1}{2}H_j^{-1}(\widetilde{\chi} + 2\widetilde{b_j}). \tag{3.5}$$

Let

$$\widetilde{I} = \begin{pmatrix} 1 \\ 1 \end{pmatrix},$$

the constraint equations can be written in the matrix format. That is

$$\sum_{j=1}^{n} \widetilde{w_j} = \sum_{j=1}^{n} \frac{1}{2}H_j^{-1}(\widetilde{\chi} + 2\widetilde{b_j}) = \widetilde{I},$$

we can solve for $\widetilde{\chi}$, which is given by

$$\widetilde{\chi} = 2(\sum_{j=1}^{n} H_j^{-1})^{-1}\left[\widetilde{I} - \left(\sum_{j=1}^{n} H_j^{-1}\widetilde{b_j}\right)\right]. \tag{3.6}$$

Next, plugging (3.6) into (3.5), we obtain the optimal weights as

$$\widetilde{w_j} = H_j^{-1}\left[\left(\sum_{j=1}^{n} H_j^{-1}\right)^{-1}\widetilde{I} - \left(\sum_{j=1}^{n} H_j^{-1}\right)^{-1}\left(\sum_{j=1}^{n} H_j^{-1}\widetilde{b_j}\right) + \widetilde{b_j}\right]. \tag{3.7}$$

The optimal weights involve the unknown parameters, which can be consistently estimated from estimated transformed data $(\hat{U}_{ijl}, \hat{V}_{ij})$

$$\hat{U}_{ijl} = \hat{G}_i(x_{ijl}), \hat{V}_{ij} = \hat{F}_i(y_{ij}),$$

The estimates of unknown parameters calculated from the estimated transformed data are

given as

$$\begin{aligned}
\hat{\sigma}_{ll'}^{u_1u_1} &= \frac{\sum_{j=1}^{n}\delta_{1jl}\delta_{1jl'}(\hat{U}_{1jl}-\bar{U}_{1l})(\hat{U}_{1jl'}-\bar{U}_{1l'})}{\sum_{j=1}^{n}\delta_{1jl}\delta_{1jl'}},\\
\hat{\sigma}_{ll'}^{u_2u_2} &= \frac{\sum_{j=1}^{n}\delta_{2jl}\delta_{2jl'}(\hat{U}_{2jl}-\bar{U}_{2l})(\hat{U}_{2jl'}-\bar{U}_{2l'})}{\sum_{j=1}^{n}\delta_{2jl}\delta_{2jl'}},\\
\hat{\sigma}_{kl}^{u_1u_2} &= \frac{\sum_{j=1}^{n}\delta_{1jk}\delta_{2jl}(\hat{U}_{1jk}-\bar{U}_{1k})(\hat{U}_{2jl}-\bar{U}_{2l})}{\sum_{j=1}^{n}\delta_{1jk}\delta_{2jl}},\\
\hat{\sigma}_{l}^{u_1v_1} &= \frac{\sum_{j=1}^{n}\delta_{1jl}\delta_{1j}(\hat{U}_{1jl}-\bar{U}_{1l})(\hat{V}_{1j}-\bar{V}_{1})}{\sum_{j=1}^{n}\delta_{1jl}\delta_{1j}},\\
\hat{\sigma}_{l}^{u_1v_2} &= \frac{\sum_{j=1}^{n}\delta_{1jl}\delta_{2j}(\hat{U}_{1jl}-\bar{U}_{1l})(\hat{V}_{2j}-\bar{V}_{2})}{\sum_{j=1}^{n}\delta_{1jl}\delta_{2j}},\\
\hat{\sigma}_{l}^{u_2v_2} &= \frac{\sum_{j=1}^{n}\delta_{2jl}\delta_{2j}(\hat{U}_{2jl}-\bar{U}_{2l})(\hat{V}_{2j}-\bar{V}_{2})}{\sum_{j=1}^{n}\delta_{2jl}\delta_{2j}},\\
\hat{\sigma}_{l}^{u_2v_1} &= \frac{\sum_{j=1}^{n}\delta_{2jl}\delta_{1j}(\hat{U}_{2jl}-\bar{U}_{2l})(\hat{V}_{1j}-\bar{V}_{1})}{\sum_{j=1}^{n}\delta_{2jl}\delta_{1j}},\\
\hat{\sigma}^{v_1v_1} &= \frac{\sum_{j=1}^{n}\delta_{1j}(\hat{V}_{1j}-\bar{V}_{1})(\hat{V}_{1j}-\bar{V}_{1})}{\sum_{j=1}^{n}\delta_{1j}},\\
\hat{\sigma}^{v_2v_2} &= \frac{\sum_{j=1}^{n}\delta_{2j}(\hat{V}_{2j}-\bar{V}_{2})(\hat{V}_{2j}-\bar{V}_{2})}{\sum_{j=1}^{n}\delta_{2j}},\\
\hat{\sigma}^{v_1v_2} &= \frac{\sum_{j=1}^{n}\delta_{1j}\delta_{2j}(\hat{V}_{1j}-\bar{V}_{1})(\hat{V}_{2j}-\bar{V}_{2})}{\sum_{j=1}^{n}\delta_{1j}\delta_{2j}},
\end{aligned}$$

where $\delta_{ijl}=1$ if the jth subject in the ith group has the lth non-progression visit and =0 otherwise; $\delta_{ij}=1$ if the jth subject in the ith group has the disease progression visit and =0 otherwise; $\bar{U}_{ijl}=\sum_{j=1}^{n}\delta_{ijl}\hat{U}_{ijl}/\sum_{j=1}^{n}\delta_{ijl}$ and $\bar{V}_{ij}=\sum_{j=1}^{n}\delta_{ij}\hat{V}_{ij}/\sum_{j=1}^{n}\delta_{ij}$ and so on. The estimated optimal weights are then obtained by plugging those estimates into (3.7). Since $\hat{G}_i(x_{ijl})$ includes w_{ij}, we may iteratively estimate w_{ij} and $G_i(.)$ until it converges, or, to allow for a closed-form solution, we may replace $\hat{w}_{ij}$ in $\hat{G}_i(x_{ijl})$ with any simple weight such as $w_{ij}=m_{ij}/\sum_{j'=1}^{n}m_{ij'}$ or $w_{ij}=1/n$.

Now consider three special cases: (1) there is no within-subject correlation between any two time points, $\rho_{u1u1}=\rho_{u1v1}=0$ and $\rho_{u2u2}=\rho_{u2v2}=0$. In this case, the optimal weight becomes $w_{ij}=m_{ij}/\sum_{j'=1}^{n}m_{ij'}$, which means that the simple weighting scheme 1 suggested by Emir et al. (2000) is optimal; (2) there is perfect within-subject correlation between any two time points, $\rho_{u1u1}=\rho_{u1v1}=1$ and $\rho_{u2u2}=\rho_{u2v2}=1$. In this case, the optimal weight becomes $w_{ij}=1/D_i$ for subject j in group i who became a progressor at some time point, and $w_{ij}=0$ for subject j in group i who remained a non-progressor until the end of study, which means that the simple weighting scheme 2 suggested by Emir et al. (2000) is not optimal unless $D_i=n$, that is, all subjects in both groups became progressors at some time point during the study period; (3) there is no between-group correlation at any time point, $\rho_{u1u2}=\rho_{u1v2}=\rho_{u2v1}=0$. In this case, the weights by Wu et al. (2011) are not optimal unless the number of visits and disease incidence rates are the same in two groups.

4 Asymptotic variance and the relative efficiency

Let $\tau_1 = \lim_{n\to\infty} D_1/n$, and $\tau_2 = \lim_{n\to\infty} D_2/n$, so τ_1 and τ_2 are the disease incidence rates in group 1 and 2 respectively. Let $\hat{\Delta}_1$ be the estimator of Δ using simple weighting scheme $w_{1j} = m_{1j}/\sum_{j'=1}^{n} m_{1j'}$ and $w_{2j} = m_{2j}/\sum_{j'=1}^{n} m_{2j'}$; and $\hat{\Delta}_2$ be the estimator of Δ using simple weighting scheme $w_{1j} = 1/n$ and $w_{2j} = 1/n$. To compare our optimal estimator with $\hat{\Delta}_1$ and $\hat{\Delta}_2$, we consider the asymptotic variances of $\hat{\Delta}_1$ and $\hat{\Delta}_2$.

Emir et al. (2000) proved that $\hat{\Delta}/\sqrt{Var(\hat{\Delta})}$ is approximately normal with $N(0,1)$. We can show that $\sqrt{n}(\hat{\Delta}_1 - \Delta)$ is approximately normal with $N(0, \sigma_1^2)$

$$\begin{aligned}\sigma_1^2 &= \frac{E\sum_{l,l'=1}^{m_{1j}} \sigma_{ll'}^{u_1u_1}}{(Em_1)^2} - 2\frac{E\sum_{k=1}^{m_{1j}}\sum_{l=1}^{m_{2j}} \sigma_{kl}^{u_1u_2}}{(Em_1)(Em_2)} + \frac{E\sum_{l,l'=1}^{m_{2j}} \sigma_{ll'}^{u_2u_2}}{(Em_2)^2} \\ &\quad -2\frac{E\sum_{l=1}^{m_{1j}} \sigma_{l}^{u_1v_1}}{Em_1} + 2\frac{E\sum_{l=1}^{m_{1j}} \sigma_{l}^{u_1v_2}}{Em_1} - 2\frac{E\sum_{l=1}^{m_{2j}} \sigma_{l}^{u_2v_2}}{Em_2} + 2\frac{E\sum_{l=1}^{m_{2j}} \sigma_{l}^{u_2v_1}}{Em_2} \\ &\quad +\tau_1^{-1}\sigma^{v_1v_1} + \tau_2^{-1}\sigma^{v_2v_2},\end{aligned} \tag{4.1}$$

where $m_i = \frac{1}{n}\sum_{j=1}^{n} m_{ij}$ and E is the expected value taken with respect to the random variable of m_{ij}.

Similarly, we can also show that $\sqrt{n}(\hat{\Delta}_2 - \Delta)$ is approximately normal with $N(0, \sigma_2^2)$

$$\begin{aligned}\sigma_2^2 &= E\frac{\sum_{l,l'=1}^{m_{1j}} \sigma_{ll'}^{u_1u_1}}{m_1^2} - 2E\frac{\sum_{k=1}^{m_{1j}}\sum_{l=1}^{m_{2j}} \sigma_{kl}^{u_1u_2}}{m_1m_2} + E\frac{\sum_{l,l'=1}^{m_{2j}} \sigma_{ll'}^{u_2u_2}}{m_2^2} \\ &\quad -2E\frac{\sum_{l=1}^{m_{1j}} \sigma_{l}^{u_1v_1}}{m_1} + 2E\frac{\sum_{l=1}^{m_{1j}} \sigma_{l}^{u_1v_2}}{m_1} - 2E\frac{\sum_{l=1}^{m_{2j}} \sigma_{l}^{u_2v_2}}{m_2} + 2E\frac{\sum_{l=1}^{m_{2j}} \sigma_{l}^{u_2v_1}}{m_2} \\ &\quad +\tau_1^{-1}\sigma^{v_1v_1} + \tau_2^{-1}\sigma^{v_2v_2}.\end{aligned} \tag{4.2}$$

Let $\hat{\Delta}_{op}$ be the estimate of Δ obtained by using the estimated optimal weights. We can show that $\sqrt{n}(\hat{\Delta}_{op} - \Delta)$ is approximately normal with mean 0 and variance

$$\sigma_{op}^2 = \left(\widetilde{I}^t - \widetilde{\phi}^t\right)\Sigma^{-1}\left(\widetilde{I} - \widetilde{\phi}\right) - \upsilon + \tau_1^{-1}\sigma^{v_1v_1} + \tau_2^{-1}\sigma^{v_2v_2}, \tag{4.3}$$

where

$$\widetilde{\phi} = \begin{pmatrix} e_1 \\ e_2 \end{pmatrix},$$

$$
\begin{aligned}
e_1 &= \lim_{n\to\infty}\sum_{j=1}^{n}\frac{a_{2j}b_{1j}+b_{2j}c_j}{a_{1j}a_{2j}-c_jc_j} \\
&= {\tau_1}^{-1}E\frac{m_1\left(\sum_{l=1}^{m_{1j}}\sigma_l^{u_1v_1}-\sum_{l=1}^{m_{1j}}\sigma_l^{u_1v_2}\right)\sum_{l,l'=1}^{m_{2j}}\sigma_{ll'}^{u_2u_2}}{\sum_{l,l'=1}^{m_{1j}}\sigma_{ll'}^{u_1u_1}\sum_{l,l'=1}^{m_{2j}}\sigma_{ll'}^{u_2u_2}-\left(\sum_{k=1}^{m_{1j}}\sum_{l=1}^{m_{2j}}\sigma_{kl}^{u_1u_2}\right)^2} \\
&\quad +{\tau_2}^{-1}E\frac{m_1\left(\sum_{l=1}^{m_{2j}}\sigma_l^{u_2v_2}-\sum_{l=1}^{m_{2j}}\sigma_l^{u_2v_1}\right)\sum_{k=1}^{m_{1j}}\sum_{l=1}^{m_{2j}}\sigma_{kl}^{u_1u_2}}{\sum_{l,l'=1}^{m_{1j}}\sigma_{ll'}^{u_1u_1}\sum_{l,l'=1}^{m_{2j}}\sigma_{ll'}^{u_2u_2}-\left(\sum_{k=1}^{m_{1j}}\sum_{l=1}^{m_{2j}}\sigma_{kl}^{u_1u_2}\right)^2}, \\
e_2 &= \lim_{n\to\infty}\frac{1}{n}\sum_{j=1}^{n}\frac{a_{1j}b_{2j}+b_{1j}c_j}{a_{1j}a_{2j}-c_jc_j} \\
&= {\tau_2}^{-1}E\frac{m_2\left(\sum_{l=1}^{m_{2j}}\sigma_l^{u_2v_2}-\sum_{l=1}^{m_{2j}}\sigma_l^{u_2v_1}\right)\sum_{l,l'=1}^{m_{1j}}\sigma_{ll'}^{u_1u_1}}{\sum_{l,l'=1}^{m_{1j}}\sigma_{ll'}^{u_1u_1}\sum_{l,l'=1}^{m_{2j}}\sigma_{ll'}^{u_2u_2}-\left(\sum_{k=1}^{m_{1j}}\sum_{l=1}^{m_{2j}}\sigma_{kl}^{u_1u_2}\right)^2} \\
&\quad +{\tau_1}^{-1}E\frac{m_2\left(\sum_{l=1}^{m_{1j}}\sigma_l^{u_1v_1}-\sum_{l=1}^{m_{1j}}\sigma_l^{u_1v_2}\right)\sum_{k=1}^{m_{1j}}\sum_{l=1}^{m_{2j}}\sigma_{kl}^{u_1u_2}}{\sum_{l,l'=1}^{m_{1j}}\sigma_{ll'}^{u_1u_1}\sum_{l,l'=1}^{m_{2j}}\sigma_{ll'}^{u_2u_2}-\left(\sum_{k=1}^{m_{1j}}\sum_{l=1}^{m_{2j}}\sigma_{kl}^{u_1u_2}\right)^2},
\end{aligned}
$$

$$
\Sigma=\begin{pmatrix}\sigma_{11} & \sigma_{12}\\ \sigma_{21} & \sigma_{22}\end{pmatrix},
$$

$$
\begin{aligned}
\sigma_{11} &= \lim_{n\to\infty}\frac{1}{n}\sum_{j=1}^{n}\frac{a_{2j}}{a_{1j}a_{2j}-c_jc_j} \\
&= E\frac{{m_1}^2\sum_{l,l'=1}^{m_{2j}}\sigma_{ll'}^{u_2u_2}}{\sum_{l,l'=1}^{m_{1j}}\sigma_{ll'}^{u_1u_1}\sum_{l,l'=1}^{m_{2j}}\sigma_{ll'}^{u_2u_2}-\left(\sum_{k=1}^{m_{1j}}\sum_{l=1}^{m_{2j}}\sigma_{kl}^{u_1u_2}\right)^2}, \\
\sigma_{12} &= \sigma_{21}=\lim_{n\to\infty}\frac{1}{n}\sum_{j=1}^{n}\frac{c_j}{a_{1j}a_{2j}-c_jc_j} \\
&= E\frac{m_1m_2\sum_{k=1}^{m_{1j}}\sum_{l=1}^{m_{2j}}\sigma_{kl}^{u_1u_2}}{\sum_{l,l'=1}^{m_{1j}}\sigma_{ll'}^{u_1u_1}\sum_{l,l'=1}^{m_{2j}}\sigma_{ll'}^{u_2u_2}-\left(\sum_{k=1}^{m_{1j}}\sum_{l=1}^{m_{2j}}\sigma_{kl}^{u_1u_2}\right)^2}, \\
\sigma_{22} &= \lim_{n\to\infty}\frac{1}{n}\sum_{j=1}^{n}\frac{a_{1j}}{a_{1j}a_{2j}-c_jc_j}, \\
&= E\frac{{m_2}^2\sum_{l,l'=1}^{m_{1j}}\sigma_{ll'}^{u_1u_1}}{\sum_{l,l'=1}^{m_{1j}}\sigma_{ll'}^{u_1u_1}\sum_{l,l'=1}^{m_{2j}}\sigma_{ll'}^{u_2u_2}-\left(\sum_{k=1}^{m_{1j}}\sum_{l=1}^{m_{2j}}\sigma_{kl}^{u_1u_2}\right)^2},
\end{aligned}
$$

and

$$
\begin{aligned}
v &= \lim_{n\to\infty} n\sum_{j=1}^{n}\frac{a_{2j}b_{1j}^2+2b_{1j}b_{2j}c_j+a_{1j}b_{2j}^2}{a_{1j}a_{2j}-c_jc_j} \\
&= \frac{1}{{\tau_1}^2}E\frac{\sum_{l,l'=1}^{m_{2j}}\sigma_{ll'}^{u_2u_2}\left(\sum_{l=1}^{m_{1j}}\sigma_l^{u_1v_1}\right)^2+\sum_{l,l'=1}^{m_{1j}}\sigma_{ll'}^{u_1u_1}\left(\sum_{l=1}^{m_{2j}}\sigma_l^{u_2v_1}\right)^2}{\sum_{l,l'=1}^{m_{1j}}\sigma_{ll'}^{u_1u_1}\sum_{l,l'=1}^{m_{2j}}\sigma_{ll'}^{u_2u_2}-\left(\sum_{k=1}^{m_{1j}}\sum_{l=1}^{m_{2j}}\sigma_{kl}^{u_1u_2}\right)^2} \\
&\quad -2\frac{1}{{\tau_1}^2}E\frac{\sum_{k=1}^{m_{1j}}\sum_{l=1}^{m_{2j}}\sigma_{kl}^{u_1u_2}\sum_{l=1}^{m_{1j}}\sigma_l^{u_1v_1}\sum_{l=1}^{m_{2j}}\sigma_l^{u_2v_1}}{\sum_{l,l'=1}^{m_{1j}}\sigma_{ll'}^{u_1u_1}\sum_{l,l'=1}^{m_{2j}}\sigma_{ll'}^{u_2u_2}-\left(\sum_{k=1}^{m_{1j}}\sum_{l=1}^{m_{2j}}\sigma_{kl}^{u_1u_2}\right)^2} \\
&\quad +\frac{1}{{\tau_2}^2}E\frac{\sum_{l,l'=1}^{m_{1j}}\sigma_{ll'}^{u_1u_1}\left(\sum_{l=1}^{m_{2j}}\sigma_l^{u_2v_2}\right)^2+\sum_{l,l'=1}^{m_{2j}}\sigma_{ll'}^{u_2u_2}\left(\sum_{l=1}^{m_{1j}}\sigma_l^{u_1v_2}\right)^2}{\sum_{l,l'=1}^{m_{1j}}\sigma_{ll'}^{u_1u_1}\sum_{l,l'=1}^{m_{2j}}\sigma_{ll'}^{u_2u_2}-\left(\sum_{k=1}^{m_{1j}}\sum_{l=1}^{m_{2j}}\sigma_{kl}^{u_1u_2}\right)^2} \\
&\quad -2\frac{1}{{\tau_2}^2}E\frac{\sum_{k=1}^{m_{1j}}\sum_{l=1}^{m_{2j}}\sigma_{kl}^{u_1u_2}\sum_{l=1}^{m_{1j}}\sigma_l^{u_1v_2}\sum_{l=1}^{m_{2j}}\sigma_l^{u_2v_2}}{\sum_{l,l'=1}^{m_{1j}}\sigma_{ll'}^{u_1u_1}\sum_{l,l'=1}^{m_{2j}}\sigma_{ll'}^{u_2u_2}-\left(\sum_{k=1}^{m_{1j}}\sum_{l=1}^{m_{2j}}\sigma_{kl}^{u_1u_2}\right)^2} \\
&\quad +2\frac{1}{\tau_1\tau_2}E\frac{\sum_{k=1}^{m_{1j}}\sum_{l=1}^{m_{2j}}\sigma_{kl}^{u_1u_2}\left(\sum_{l=1}^{m_{1j}}\sigma_l^{u_1v_1}\sum_{l=1}^{m_{2j}}\sigma_l^{u_2v_2}+\sum_{l=1}^{m_{1j}}\sigma_l^{u_1v_2}\sum_{l=1}^{m_{2j}}\sigma_l^{u_2v_1}\right)}{\sum_{l,l'=1}^{m_{1j}}\sigma_{ll'}^{u_1u_1}\sum_{l,l'=1}^{m_{2j}}\sigma_{ll'}^{u_2u_2}-\left(\sum_{k=1}^{m_{1j}}\sum_{l=1}^{m_{2j}}\sigma_{kl}^{u_1u_2}\right)^2} \\
&\quad -2\frac{1}{\tau_1\tau_2}E\frac{\sum_{l,l'=1}^{m_{1j}}\sigma_{ll'}^{u_1u_1}\sum_{l=1}^{m_{2j}}\sigma_l^{u_2v_2}\sum_{l=1}^{m_{2j}}\sigma_l^{u_2v_1}+\sum_{l,l'=1}^{m_{2j}}\sigma_{ll'}^{u_2u_2}\sum_{l=1}^{m_{1j}}\sigma_l^{u_1v_1}\sum_{l=1}^{m_{1j}}\sigma_l^{u_1v_2}}{\sum_{l,l'=1}^{m_{1j}}\sigma_{ll'}^{u_1u_1}\sum_{l,l'=1}^{m_{2j}}\sigma_{ll'}^{u_2u_2}-\left(\sum_{k=1}^{m_{1j}}\sum_{l=1}^{m_{2j}}\sigma_{kl}^{u_1u_2}\right)^2}.
\end{aligned}
$$

Let $ARE_1 = \sigma_{op}^2/\sigma_1^2$ be the asymptotic relative efficiency for comparing $\hat{\Delta}_1$ with $\hat{\Delta}_{op}$, and $ARE_2 = \sigma_{op}^2/\sigma_2^2$ be the asymptotic relative efficiency for comparing $\hat{\Delta}_2$ with $\hat{\Delta}_{op}$. To demonstrate how the within-subject correlation, the between-group correlation, and the incidence of disease affect ARE_1 and ARE_2, we consider a special case where variances of U_{ijl} and V_{ij} are homogeneous across visits and groups, within-subject non-progression and non-progression correlation coefficients are homogeneous across groups, within-subject progression and non-progression correlation coefficients are homogeneous across groups, and between-group correlation coefficients are homogeneous across visits. Specifically,

$$
\begin{aligned}
Var(U_{ijl}) &= Var(V_{ij}) = \sigma^2, \\
Corr(U_{ijl}, U_{ijl'}) &= Corr(U_{ijl}, V_{ij}) = \rho_w, \\
Corr(U_{ijl}, U_{i'jl}) &= Corr(U_{ijl}, V_{i'j}) = \rho_b, i \neq i'.
\end{aligned}
$$

We graph ARE_1 and ARE_2 against ρ_w for three different values of ρ_b, $\rho_b = 0.3, 0.5, 0.7$ and three different sets of (τ_1, τ_2), $(\tau_1, \tau_2) = (0.5, 0.5), (0.3, 0.3), (0.1, 0.1)$. The uniform distribution of m_1, $P(m_1 = k) = 1/6, k = 1, \cdots, 6$, and the distribution of m_2, $P(m_2 = k) = 1/3, 1/3, 1/3, 0, 0, 0$, were used to calculate the expectations involved in ARE_1 and ARE_2. Figure 1 shows that the efficiency gain of our optimal estimator increases dramatically as ρ_w increases and (τ_1, τ_2) decreases, and increases as ρ_b increases. The loss of efficiency by using the two simple weighting schemes instead of our optimal weights can be severe when the within-subject correlation is large and the incidence of disease is small.

5 Simulation results

Simulations were conducted to examine the finite sample properties of the proposed weighting scheme relative to the simple weight scheme 1 and the simple weight scheme 2 sug-

gested by Emir et al. (2000) with small sample size. In the absence of disease progression, the subjects will have the biomarker observed every month for a total of at most six monthly visits per subject. For each pair of subjects, we generate an independent multivariate normal random vector $X_i = (X_{11}, X_{12}, \cdots, X_{16}, X_{21}, X_{22}, \cdots, X_{26})$, of size $12 \times n$ with mean vector 0 and variance-covariance matrix $\Sigma = (\sigma_{ll'})_{12\times 12}$ with

$$\sigma_{ll'} = \begin{cases} 1 & \text{if } l = l' \\ \gamma & \text{if } l, l' = 1, ..., 6 \text{ or } l, l' = 7, ..., 12 \\ \lambda & \text{if } l = 1, ..., 6; l' = 7, ..., 12 \text{ or } l = 7, ..., 12; l' = 1, ..., 6. \end{cases}$$

Note that $(X_{11}, X_{12}, \cdots, X_{16})$ are the observed biomarker values for the subjects in the exposed group and $(X_{21}, X_{22}, \cdots, X_{26})$ for the matched subjects in the non-exposed group, and that γ and λ are the parameters which introduce correlations within-subject and between-group respectively. The values of λ and γ were chosen so that the variance-covariance matrix Σ is positive definite.

We generate disease onset times for the subjects using an exponential distribution such that the expected disease rates at six months in two groups are ψ_1 and ψ_2. If a simulated disease onset time is greater than six months, we define the subject to be a non-progressor at all six visits and use all six values of X_i for the biomarker. If the disease onset time occurs before six months, we assume that the disease progession is detected clinically at the next visit. For example, if a disease onset in the exposed group occurs between the third and fourth visit, the simulated biomarker values for the first three visits are (x_{11}, x_{12}, x_{13}). We assume the expected value of the biomarker is increased by 1 at the time of disease onset, so we define the biomarker value at this fourth visit to be $Y_1 = x_{14} + 1$. With this set-up for both groups, the true AUC is equal to 0.75 in both groups and the true AUC difference of the biomarker between groups is $\Delta = 0$. In our simulation, we set the disease rates to be either equal or unequal between groups using $(\psi_1, \psi_2) = (0.5, 0.4), (0.4, 0.4), (0.2, 0.4)$. The disease rates were chosen to show how the change of disease rate in any group would impact the efficency. The correlations were either low, moderate or high, using $\gamma = 0.3, 0.5, 0.7, 0.9$ and $\lambda = 0.0, 0.3, 0.5, 0.7$. The sample size of 50 and the sample size of 100 per group were considered for each combination of$(\lambda, \gamma, \psi_1, \psi_2)$.

A total of 2000 simulations were replicated. The efficiency of the estimators was estimated using the mean square error (MSE), which was computed using the variance of the parameter estimates and the estimated bias. Table 2 (n=50) summarizes the results using the relative efficiency. The results are consistent between both sample sizes. These simulations show that the estimator using optimal weights outperforms both $\hat{\Delta}_1$ and $\hat{\Delta}_2$ especially when the within-group correlation is large, which is consistent with the conclusion from the asymptotic comparisons. As well, the performance is increasing as the between-group correlation increases and the disease incidence rate decreases. Additionally, we also compared the optimal weights to the weights using Wu et al.'s method (2011). The results (RE_3) indicate up to 20% of efficiency gain when the between-group correlation is being taken account in the optimal weights.

6 Application on the thyroidism study data

The association between thyroid disorders and risk of breast cancer has long been a subject of debate. SunCoast CCOP Research Base at the University of South Florida is conducting a matched-subject design trial to study thyroid function and breast cancer: A pilot study to estimate the prevalence of thyroid dysfunction in women diagnosed with breast cancer

Table 1: Results for Comparing Accuracy of TPOAb in Predicting Thyroid Function.

	Optimal Weight	Simple Weight 1	Simple Weight 2
Estimate	-0.014	-0.031	-0.030
Variance	0.0016	0.0025	0.0023
Relative efficiency	1	0.64	0.70

and the magnitude of change in thyroid function post-chemotherapy. Two hundred and fifty breast cancer patients between ages of 25 and 75, diagnosed with primary, operable, stage I-III B breast cancer with planned chemotherapy regimen Adriamycin/Cytoxan (AC) plus a taxane were the trial candidates. Two hundred and fifty healthy voluteers, from the same general demographic area, without prior history of cancer and within 5 years of the patient's age (+/- 5 years) were matched for each cancer patient. All subjects were followed for two years or until disease onset. All biomarkers were collected at baseline, yearly, and at the end of study. Free T4 and TSH have been identified as reliable and the most effective tool for diagnosing thyroid function. They are used to define the status of hypothyroidism as the gold standard. The antibody TPO is a useful biomarker for establishing the presence of thyroid autoimmunity as the cause of hypothyroidism. Previous studies have shown that the higher the TPOAb concentration, the more rapid the development of hypothyroidism. If the women with breast cancer are at higher risk of having thyroid disorders or changes in antibody level that might result in worsened hypothyroidism, it is important to understand the mechanism of these changes. The characterization of prediction accuracy is essential to the success of future prevention trials for thyroidism disorder among the women with breast cancer. Of particular interests, clinicians hypothesized that the breast cancer may alter the performance of TPO antibody titers in predicting thyroidism disorder.

The study is ongoing. The use of this data is for illustration of statistical methods only. It does NOT represent the final outcome reporting of the ongoing study. In this illustrative example, only 213 pairs of subjects who completed the study as 05/01/2012 and had at least one measurement were included. Hypothyroidism is defined using arbitrary thresholds, with TSH greater than 2.2 mIU/L and Free T4 less than 1.76 pmol/L. The incidence rate of hypothyriodism was only 12% in the brease cancer group and approximate 9% in health control group during the study period.

The raw values of TPOAb titers were treated as the original data of (x_{1jl}, y_{1j}) for the breast cancer group and (x_{2jl}, y_{2j}) for the heathy control group. The optimal weights were obtained by following these procedures: First, obtain the estimates of F_i and G_i using simple weight 1; second, generate the transformed data $(\hat{u}_{ijl}, \hat{v}_{ij})$; next, obtain the estimates of $\sigma^{u_i u_i}$, $\sigma^{u_i v_i}$ and $\sigma^{v_i v_i}$ from the transformed data; finally, plug these estimated variance-covariance parameters into (3.7) to get the estimated optimal weights. The estimated optimal weights were then plugged into equation (2.1) to calculate the point estimate of the two AUCs difference and plugged into (3.3) to calculate the variance of $\hat{\Delta}_{op}$. Table 1 summarizes both the point estimates and their variance estimates using all three weight schemes. The optimal weight scheme outperformed the other two simple weight schemes with a substantial gain of efficiency because the disease incidence rates were low in both groups and the within-subject correlation was moderate to high in this study.

7 Concluding remarks

In previous studies, the Cox proportional hazard regression model with a time-dependent covariant was traditionally utilized for evaluating the biomarker with repeated measurements (Cox, 1972; Kalbfleisch, 1980). However, when the samples are correlated, the Cox proportional hazard model cannot be used. There has been an increased use of the ROC curve to examine the prognostic performance of some continuous biomarkers with repeated measurements. A non-parametric ROC approach, due to Emir et al. (2000) was introduced to estimate area under the ROC curve of a repeated biomarker. We modified Emir et al.'s approach (2000) to compare the prediction accuracy of a biomarker between two correlated groups. When the study subjects are limited and cost is high, the efficiency of the statistical methods is a crucial consideration when designing clinical studies. We extended Wu et al.'s idea (2011) to provide a solution to weight optimization which minimize the variance of AUCs comparison estimate. Our simulation results show substantial gains of efficiency by using an optimal weighting scheme when the correlation within subject is high, the correlation between groups is high, and/or the disease incidence rate is low. The proposed optimal weighting scheme is generally preferred to the two weighting schemes suggested by Emir et al. (2000). Thus, it is recommended.

This research has several limitations. First, the optimal weights could be out of boundary when the sample size is too small. Secondly, the homogenous variance-covariance structure was used in the simulation studies. In the future study, we may consider other more complicated structure. The methodology presented in this paper focused on comparing the predictive accuracies of a repeated biomarker between two correlated groups in the one to one matched-subject design study. This methodology may be adapted to compare AUCs in matched-subject design studies when there are more than one matches per subject. As well, the methodology can be applied to other correlated-group design study, such as cross-over design study. Futhermore, the extension of the proposed methodology can be used to accommodate the clustered data, such as there are recurrent outcome events. Future research of these, based on the weighting optimization methods described here, may produce better solutions, particularly where the efficiecy is concerned.

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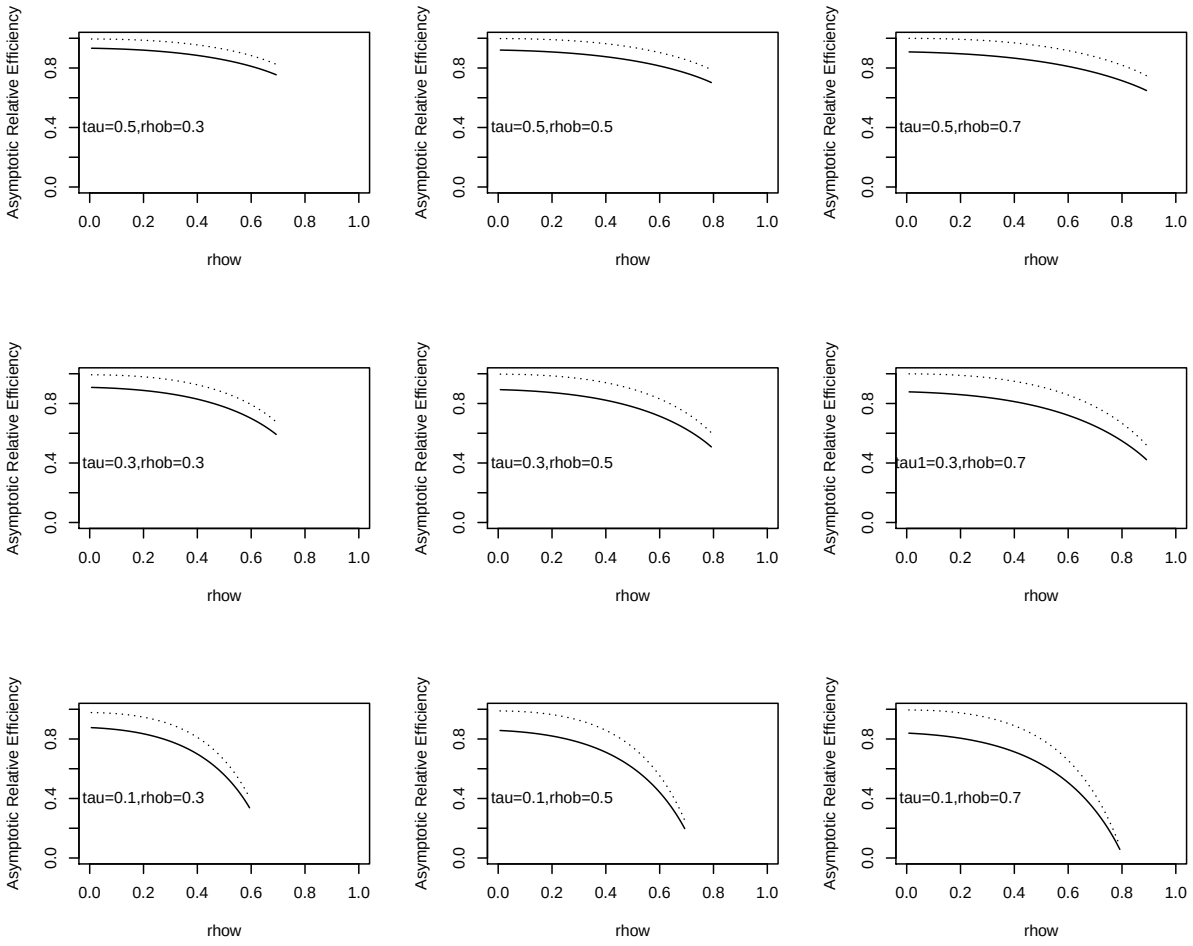

Figure 1: The Effect of Within-subject Correlation Coefficient(rhow), Between-group Correlation Coefficient(rhob), and the Incidence Rate of Disease(tau) on the Asymptotic Relative Efficiencies, ARE_1 (Solid Line) and ARE_2 (Broken Line).

Table 2: Simulation Results for AUCs Comparison (n=50)

n	ψ_1	ψ_2	λ	γ	RE_1	RE_2	RE_3
50	0.5	0.4	0.0	0.3	0.92	0.95	0.99
50	0.5	0.4	0.0	0.5	0.89	0.90	0.99
50	0.5	0.4	0.0	0.7	0.85	0.88	0.97
50	0.5	0.4	0.0	0.9	0.76	0.79	0.97
50	0.5	0.4	0.3	0.3	0.90	0.91	0.96
50	0.5	0.4	0.3	0.5	0.88	0.89	0.97
50	0.5	0.4	0.3	0.7	0.83	0.85	0.97
50	0.5	0.4	0.3	0.9	0.77	0.80	0.97
50	0.5	0.4	0.5	0.3	0.84	0.85	0.87
50	0.5	0.4	0.5	0.5	0.86	0.87	0.93
50	0.5	0.4	0.5	0.7	0.84	0.86	0.98
50	0.5	0.4	0.5	0.9	0.78	0.80	0.97
50	0.5	0.4	0.7	0.3	0.82	0.83	0.88
50	0.5	0.4	0.7	0.5	0.81	0.82	0.90
50	0.5	0.4	0.7	0.7	0.80	0.82	0.89
50	0.5	0.4	0.7	0.9	0.79	0.81	0.96
50	0.4	0.4	0.0	0.3	0.90	0.92	0.99
50	0.4	0.4	0.0	0.5	0.84	0.86	0.98
50	0.4	0.4	0.0	0.7	0.80	0.85	0.98
50	0.4	0.4	0.0	0.9	0.72	0.73	0.97
50	0.4	0.4	0.3	0.3	0.88	0.89	0.94
50	0.4	0.4	0.3	0.5	0.86	0.87	0.95
50	0.4	0.4	0.3	0.7	0.78	0.80	0.97
50	0.4	0.4	0.3	0.9	0.71	0.72	0.97
50	0.4	0.4	0.5	0.3	0.79	0.80	0.86
50	0.4	0.4	0.5	0.5	0.79	0.81	0.90
50	0.4	0.4	0.5	0.7	0.80	0.82	0.93
50	0.4	0.4	0.5	0.9	0.73	0.75	0.96
50	0.4	0.4	0.7	0.3	0.75	0.76	0.82
50	0.4	0.4	0.7	0.5	0.77	0.78	0.87
50	0.4	0.4	0.7	0.7	0.78	0.79	0.91
50	0.4	0.4	0.7	0.9	0.72	0.74	0.94
50	0.2	0.4	0.0	0.3	0.79	0.80	0.97
50	0.2	0.4	0.0	0.5	0.72	0.77	0.93
50	0.2	0.4	0.0	0.7	0.61	0.64	0.92
50	0.2	0.4	0.0	0.9	0.49	0.51	0.92
50	0.2	0.4	0.3	0.3	0.78	0.79	0.88
50	0.2	0.4	0.3	0.5	0.72	0.74	0.92
50	0.2	0.4	0.3	0.7	0.54	0.55	0.91
50	0.2	0.4	0.3	0.9	0.47	0.48	0.89
50	0.2	0.4	0.5	0.3	0.63	0.63	0.74
50	0.2	0.4	0.5	0.5	0.67	0.68	0.83
50	0.2	0.4	0.5	0.7	0.56	0.58	0.84
50	0.2	0.4	0.5	0.9	0.51	0.52	0.90
50	0.2	0.4	0.7	0.3	0.59	0.59	0.68
50	0.2	0.4	0.7	0.5	0.62	0.64	0.75
50	0.2	0.4	0.7	0.7	0.61	0.63	0.84
50	0.2	0.4	0.7	0.9	0.43	0.44	0.82