WITHIN-CLUSTER RESAMPLING METHODS
FOR CLUSTERED RECEIVER OPERATING CHARACTERISTIC (ROC) DATA

by

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Dedication

I dedicate this dissertation to my parents, Mr. Zheng Miao and Mrs. Jie Liu and my academic advisor, Dr. Liansheng Tang.

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Abstract

WITHIN-CLUSTER RESAMPLING METHODS FOR CLUSTERED RECEIVER OPERATING CHARACTERISTIC (ROC) DATA

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The diagnostic studies in which each patient has several diseased and nondiseased observations generate clustered ROC data. Within the same cluster, observations are naturally correlated, and the cluster size may be random. The traditional ROC methods on clustered data can result in a biased variance estimator and subsequently lead to incorrect statistical inference. We introduce resampling methods on clustered ROC data to account for the within-cluster correlation. The within-cluster resampling ROC methods work as follows. First, one observation is randomly selected from each patient/cluster, and then the traditional ROC methods are applied on the resampled data to obtain resampled ROC estimates. These steps are performed many times and the average of resampled ROC estimates is the final estimator. The proposed methods do not require a specific within-cluster correlation structure and yield valid estimators while accounting for the within-cluster correlation. We compare the proposed methods with existing methods in extensive simulation studies and apply the proposed methods to two eye rating examples.

Chapter 1: Background and Literature Review

1.1 Introduction

The receiver operating characteristic (ROC) curve, which is commonly used in medical diagnostic studies, is a plot of the true positive rate (TPR) (i.e. probability of identifying a case when the subject is truly diseased) versus false positive rate (FPR) (i.e. probability of identifying a case when the subject is not diseased) at different possible thresholds. The ROC curve is widely used in radiology, psychophysical and medical imaging research for detection performance, military monitoring, and industrial quality control (Metz 1978). The ROC curve indicates the trade-off between the TPR and FPR under different thresholds. It has many advantages and overcomes the limitation of using isolated measurements of TPR and FPR. The ROC curve is plotted by connecting all the points generated by possible thresholds (Zhou, Mcclish, and Obuchowski 2002).

In the mathematical notation, TPR is given by $P(T > c|D = 1)$ and FPR is given by $P(T > c|D = 0)$, where c denotes the threshold, T denotes the biomarker results and D is the indicator for disease status with 1 being a case and 0 being a control. A biomarker with 100% TPR and 0% FPR is a perfect predictor, i.e., all the case patients have positive biomarker results and all the control patients have negative biomarker results.

The most commonly used measure is the area under the ROC curve (AUC). Other measures includes the TPR at a fixed FPR, the partial area under the ROC curve (pAUC) and the likelihood ratios. Most ROC curves are concave and above the chance diagonal which is the line segment between $(0, 0)$ and $(1, 1)$. However, some of them are below the chance diagonal and are called improper curves (Hanley and McNeil 1982). The AUC between 0.5 and 1 indicates that the diagnostic biomarker has a good performance on detecting the case condition and control condition. The closer the curve is to the left upper corner, the larger the ROC curve area is and the better ability of the diagnostic biomarker has. The perfect biomarker has an AUC of 1.

In Figure 1.1, the ROC curves are for three biomarkers. The dotted ROC curve of biomarker 1 has the AUC of 0.9. The dashed ROC curve of biomarker 2 has the AUC of 0.7 and the solid ROC curve of biomarker 3 has the AUC of 0.5. Hence, biomarker 1 has the best performance on detecting the case and control condition among the three biomarkers.

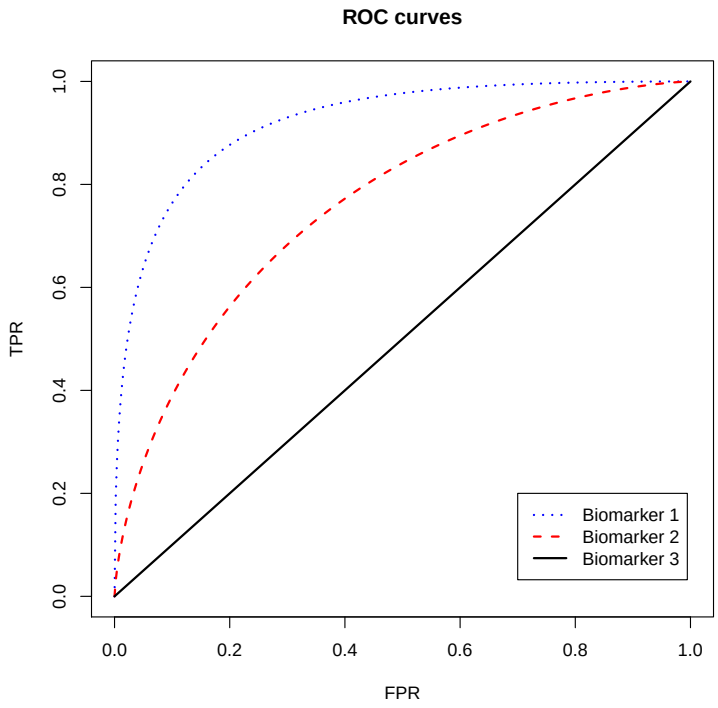

Figure 1.1: ROC curves

Much work has been considered to estimate ROC curves using independent ROC data. In this traditional setting, each subject has one biomarker result and the results are independent. Parametric and nonparametric methods are commonly used (Zhou, Mcclish, and Obuchowski 2002; DeLong, DeLong, and Clarke-Pearson 1988). A more complicated type of ROC data is clustered ROC data, in which each patient has more than one biomarker results. The biomarker results can either be from different locations on the patient or repeated results of the same location. Within each patient, the biomarker results are correlated. The results from one patient are not correlated with the results from another patient. Methods have been proposed to handle clustered ROC data, including Obuchowski's nonparametric method and Li and Zhou's unified nonparametric method (Obuchowski

1997; Li and Zhou 2008).

For clustered binary data, a novel within-cluster resampling method was originally proposed by Hoffman, Sen, and Weinberg (2001) since the generalized estimating equations (GEE) methods may not work well if the clustered binary data has different correlation structure and informative cluster size, which occurs when the cluster size is affected by the outcome (Zeger and Liang 1986; Liang and Zeger 1986). They have shown that WCR method works well with various within-cluster correlations and eliminates the effect of informative cluster size. Hoffman, Sen, and Weinberg (2001) developed the within-cluster resampling method and applied the method to angular data, Bayesian inference, p-value, vector parameters, genetics data and random cluster sizes (Follmann, Proschan, and Leifer 2003). Some authors developed Wilcoxon rank sum methods to handle the cluster effect (Rosner, Glynn, and Lee 2003; Datta and Satten 2005).

The major goal of this dissertation research is to develop a method to deal with cluster effect, including the within cluster correlation as well as an informative cluster size. We introduce within-cluster resampling methods that can take into account the within-cluster correlation of the clustered ROC data. Our methods estimate a more general class of ROC measures, and include the Wilcoxon statistic proposed by Datta and Satten (2005) as a special case.

There is a fundamental difference between our methods and existing clustered ROC methods. Our estimators based on independent observations from resampled data sets are on the patient level, while methods by Obuchowski and Li and Zhou give location level estimators. Moreover, the WCR estimator is a more meaningful estimator on measuring how accurate the diagnostic test is on patients while location level estimator is more intuitive to measure the accuracy of the diagnostic test on locations from patients. Additionally, the WCR methods generate smoother ROC curves so that a more accurate sensitivity can be estimated at a fixed false positive rate.

1.2 One ROC Curve

Evaluating the accuracy of diagnostic biomarkers is important in diagnostic medicine research. A common measure to estimate the accuracy of diagnostic biomarkers is the area under the ROC curve (AUC), which is between 0 and 1. A biomarker with the AUC close to 1 indicates a highly accurate

biomarker. A biomarker with the AUC close to 0.5 indicates a poor biomarker. The ROC curve with the AUC of 0.5 means that the diagnostic biomarker is not able to distinguish the case and control groups.

Diagnostic biomarker results can be binary, ordinal and continuous. Some biomarkers have positive and negative biomarker results under case/control conditions, which are called binary data. Some biomarkers results have some ordered values such as 1, 2, 3, which are called ordinal data (Bamber 1975). Most of the medical diagnostic biomarkers, such as biomarker results in proteomics and genetics, have continuous data (Shapiro 1999). The ROC curve is used to summarize the accuracy of biomarkers with continuous or ordinal outcomes at different chosen thresholds.

In order to assess continuous diagnostic biomarkers, three common types of ROC methodologies are commonly used, including parametric, nonparametric and semiparametric ROC methods. The parametric methods usually assume normal distributions for diagnostic biomarker results and yield a smooth ROC curves. The nonparametric ROC methods do not have distribution at requirements. The semiparametric ROC methods could generate smooth ROC curves without distribution assumptions for the biomarker results.

Denote continuous biomarker results for the ith case as $T_i^d, i = 1, \ldots, m$, which follow a distribution, F, and continuous biomarker results for the jth control as $T_j^{\bar{d}}, j = 1, \ldots, n$, which follow a distribution, G. The ROC curve plots a pair of points $(FPR(c), TPR(c))$, where c is the possible threshold, true positive rate $TPR(c) = 1 - F(c)$ and false positive rate $FPR(c) = 1 - G(c)$. The $TPR(c)$ is also denoted as a survivor function $S_D(c) = TPR(c) = P(T_i^d > c)$ and $FPR(c)$ is denoted as a survivor function $S_{\bar{D}}(c) = FPR(c) = P(T_j^{\bar{d}} > c)$. Let u be $FPR(c)$, and let $ROC(u)$ be $TPR(c)$, and $ROC(u)$ is given by

$$ROC(u) = 1 - F(G^{-1}(1-u)) = S_D(S_{\bar{D}}^{-1}(u)). \tag{1.1}$$

So the area under the ROC curve is given by

$$AUC = \int_0^1 ROC(u)du = P(T_i^d > T_j^{\bar{d}}). \tag{1.2}$$

Wieand, Gail, James, and James (1989) proposed weighted area under the curve methods to estimate the area under the curve, partial area under the curve and TPR at a fixed FPR by using the weighted average of TPRs. The weighted AUC (wAUC) is given by

$$wAUC = \int_0^1 ROC(u)dW(u), \tag{1.3}$$

where $W(u)$ is a probability measure. We let $W(u) = u$, the weighted AUC becomes AUC in Equation (1.2). Let $W(u)$ be a FPR u_0, the $wAUC$ becomes the sensitivity at FPR u_0, which is $ROC(u_0)$. Let $W(u) = (u - u_0)/(u_1 - u_0)$, $wAUC$ becomes the partial area under the curve between FPRs u_0 and u_1, which is given by

$$pAUC(u_0, u_1) = \frac{1}{u_1 - u_0} \int_{u_0}^{u_1} ROC(u)du. \tag{1.4}$$

1.2.1 Parametric Methods

One popular parametric method is the normal ROC method (Faraggi and Reiser 2002), which assumes the case and control results follow normal distributions $N(\mu_D, \sigma_D^2)$ and $N(\mu_{\bar{D}}, \sigma_{\bar{D}}^2)$, respectively. Then we have $\widehat{FPR}_{BN}(c) = 1 - \Phi((\hat{\mu}_D - c)/\hat{\sigma}_D)$ and $\widehat{TPR}_{BN}(c) = 1 - \Phi((\hat{\mu}_{\bar{D}} - c)/\hat{\sigma}_{\bar{D}})$. The ROC curve is plotted for all possible values of c and is given by

$$\widehat{ROC}_{BN}(u) = \Phi(\hat{a} + \hat{b}\Phi^{-1}(u)). \tag{1.5}$$

Therefore, we have

$$\widehat{wAUC}_{BN} = \int_0^1 \Phi(\hat{a} + \hat{b}\Phi^{-1}(u))dW(u). \tag{1.6}$$

Also the AUC is given by

$$\widehat{AUC}_{BN} = \Phi\left(\frac{\hat{a}}{\sqrt{1+\hat{b}^2}}\right), \tag{1.7}$$

where $\hat{a} = (\hat{\mu}_D - \hat{\mu}_{\bar{D}})/\hat{\sigma}_D$ and $\hat{b} = \hat{\sigma}_{\bar{D}}/\hat{\sigma}_D$. But in some of the scenarios, the biomarker measurements are not normal distributed. Zou, Tempany, Fielding, and Silverman (1998) suggested that a Box-Cox power transformation should be used to transform the original data before estimating the normal parameters and the AUC,

$$\psi_{\lambda_1}(T_i^d) = \frac{(T_i^d)^{\lambda_1} - 1}{\lambda_1}, \quad \psi_{\lambda_2}(T_j^{\bar{d}}) = \frac{(T_j^{\bar{d}})^{\lambda_2} - 1}{\lambda_2},$$

where λ_1, λ_2 are the parameters of Box-Cox transformation, $\lambda_1 \neq 0$ and $\lambda_2 \neq 0$ and could be estimated by maximum likelihood estimator.

The partial area under the ROC curve (pAUC) could be obtained when using the parametric binormal method by Jiang and Nishikawa (1996) and Thompson and Zucchini (1989). The pAUC is defined as the integral of the ROC curve between two FPRs u_0 and u_1,

$$\widehat{pAUC}_{BN}(u_0, u_1) = \int_{u_0}^{u_1} \widehat{ROC}_{BN}(u)du. \tag{1.8}$$

Hillis and Metz (2012) presented an analytic expressions for two types of pAUC. They assume, without loss of generality, the biomarker result for a control follows a standard normal distribution, that is, $\mathbf{T}^{\bar{d}} \sim N(0,1)$, and biomarker result for a case follows a normal distribution with mean μ_D

and standard deviation σ_D, that is $\mathbf{T}^d \sim N(\mu_D, \sigma_D^2)$. So that

$$pAUC(0, u_1) = F_{BVN}\left(\frac{\mu_D}{\sqrt{1+\sigma_D^2}}, \Phi^{-1}(u_1), \frac{-1}{\sqrt{1+\sigma_D^2}}\right) \tag{1.9}$$

and

$$pAUC(u_0, 1) = F_{BVN}\left(\frac{\mu_D}{\sqrt{1+\sigma_D^2}}, \Phi^{-1}(1 - ROC(u_0)), \frac{-\sigma_D}{\sqrt{1+\sigma_D^2}}\right), \tag{1.10}$$

where $F_{BVN}(t^d, t^{\bar{d}}, \rho)$ is denoted as the standardized bivariate normal distribution function with correlation ρ.

1.2.2 Nonparametric Methods

Goddard and Hinberg (1990) mentioned that if the normal distribution has been violated, the AUC obtained using the parametric binomal model would be largely biased. But the nonparametric method could overcome the distribution limitations since it does not assume distributions and could estimate the AUC directly. The nonparametric ROC method is also called the empirical ROC method. The estimated $TPR(c)$ is the proportion of subjects with biomarker results larger than or equal to a certain cutoff point c among the case subjects

$$\widehat{TPR}_{EM}(c) = \frac{1}{m}\sum_{i}^{m} I(T_i^d > c), \tag{1.11}$$

and $FPR(c)$ is estimated the proportion of subjects with biomarker results larger than a certain cutoff point c among the control subjects

$$\widehat{FPR}_{EM}(c) = \frac{1}{n}\sum_{j}^{n} I(T_j^{\bar{d}} > c). \tag{1.12}$$

Therefore, the ROC curve is given by

$$\widehat{ROC}_{EM}(u) = \frac{1}{m}\sum_{i}^{m} I[T_i^d > (1-u)\text{th percentile of } \{T_j^{\bar{d}}\}, j = 1, \ldots, n]. \tag{1.13}$$

The weighted AUC is

$$\widehat{wAUC}_{EM} = \int_0^1 \widehat{ROC}_{EM}(u) dW(u) \tag{1.14}$$

The empirical AUC can be calculated by the Mann-Whitney-Wilcoxon statistics (Hanley and McNeil 1982),

$$\widehat{AUC}_{MW} = \frac{1}{mn}\sum_{i=1}^{m}\sum_{j=1}^{n} \Psi(T_i^d, T_j^{\bar{d}}), \tag{1.15}$$

where

$$\Psi(T_i^d, T_j^{\bar{d}}) = \begin{cases} 1, & T_i^d > T_j^{\bar{d}} \\ \frac{1}{2}, & T_i^d = T_j^{\bar{d}} \\ 0, & T_i^d < T_j^{\bar{d}} \end{cases}.$$

Hence $\widehat{AUC}_{MW} = P(X > Y) + \frac{1}{2}P(X = Y)$ to adjust for ties. Hsieh and Turnbull (1996) have showed that the asymptotic properties of the empirical ROC curves and discussed the applications of the results. The advantage of this nonparametric method is its robustness, however, the estimated ROC curve is trapezoidal.

Another popular nonparametric method is a kernel smooth nonparametric method proposed by Zou, Hall, and Shapiro (1997) and Lloyd (1998). It estimates the density functions by the kernel estimator

$$\hat{F}_{KN}(t) = \frac{1}{mh}\sum_{i=1}^{m} K\left(\frac{c - T_i^d}{h}\right), \tag{1.16}$$

$$\hat{G}_{KN}(t) = \frac{1}{nh}\sum_{j=1}^{n} K\left(\frac{c - T_j^{\bar{d}}}{h}\right) \tag{1.17}$$

where c is the cutoff point, h is the kernel bandwidth and function $K(\cdot)$ is the kernel. They discussed how to choose the bandwidth h and claimed the kernel nonparametric method is robust and able to create smooth ROC curve. And they indicated that if some of the data are close to zero, a log transformation should be employed. Lloyd (1998) proposed the asymptotic expressions for variance and bias as well as the algorithm for calculating the AUC and its properties for the kernel estimator. Lloyd and Yong (1999) compared the kernel smoothing ROC estimator with the empirical estimator and concluded that the kernel estimator is more efficient and robust than empirical estimator for moderate to large sample sizes with an appropriate bandwidth. In Figure 1.2, the solid ROC curve is fitted by empirical method and the dashed ROC curve is obtained by the kernel smoothing method. They have the same AUC.

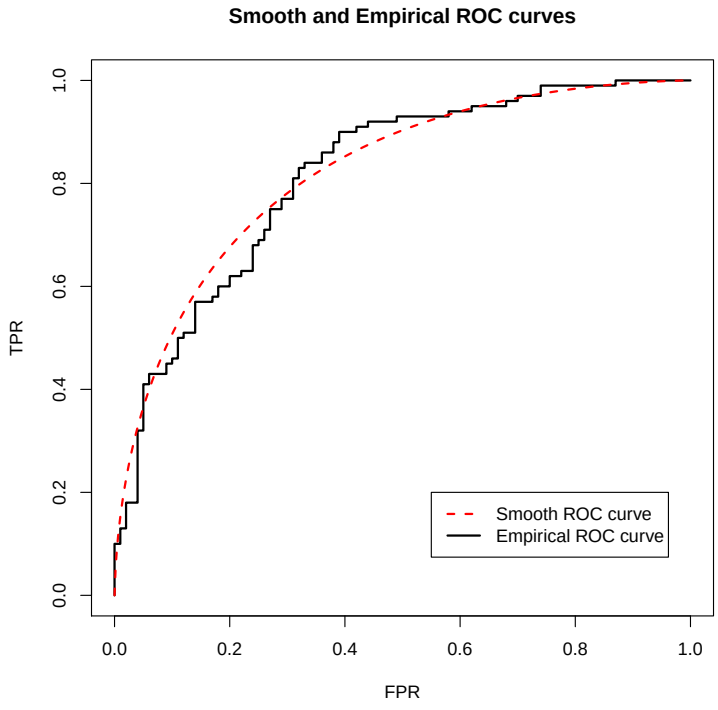

Figure 1.2: Smooth and empirical ROC curves

1.2.3 Semiparametric Methods

The third alternative method is semiparametric, which does not make any direct distribution assumptions on the biomarker results. Recently developed semiparametric methods include semiparametric binormal models, ROC logistic regression models and semiparametric kernel smoothing methods. Semiparametric binormal model is a simple semiparametric method to estimate the ROC curve. Assume T^d and $T^{\bar{d}}$ are independent but not normally distributed. After some unknown monotonic transformation H, they follow normal distributions. Without loss of generality, assume $H(t^d) \sim N(\mu_D, \sigma_D^2)$ and $H(t^{\bar{d}}) \sim N(0,1)$. A parametric model,

$$ROC_{SM}(u) = g(\beta_1 + \beta_2 h^{-1}(u)) \tag{1.18}$$

was fitted for the ROC curve after some unknown monotonic transformation for the biomarker results (Zou, Tempany, Fielding, and Silverman 1998). If we assume the binormal assumption, the semiparametric model becomes the semiparametric binormal model

$$\widehat{ROC}_{SB}(u) = \Phi(\hat{a} + \hat{b}\Phi^{-1}(u)). \tag{1.19}$$

Due to the transformation invariant property of the ROC curve, the semiparametric model has the same form as the parametric binormal model.

Many methods are developed to estimate the parameters of the binormal model. Hsieh and Turnbull (Hsieh and Turnbull 1996) have researched on the empirical ROC estimator and its asymptotic theory and proposed a generalized least squares procedure for the semiparametric binormal model as well as its asymptotic properties. The parameter a and b could be estimated by the least square method since we have a linear regression form $\Phi^{-1}(ROC_{SB}(u)) = a + b\Phi^{-1}(u)$. They compared the proposed procedure to Dorfman and Alf's MLE procedure (Dorfman and Jr. 1969) for grouped data. Zou, Tempany, Fielding, and Silverman (1998) and Zou and Hall (Zou and Hall 2000) recommended a semiparametric maximum likelihood function on the ranks of the combined

biomarker results based on the Hoeffding Theorem (Hoeffding 1948) and the two sample rank procedures to estimate the parameters. Metz, Herman, Shen, et al. (1998) proposed to categorize the ordered raw biomarker results data and estimate the binormal parameters by applying Dorfman-Alf method. They proposed two algorithms, LABROC4 algorithm, a true maximum likelihood estimation, and LABROC5 algorithm, a quasi maximum likelihood estimation. Cai and Moskowitz (2004) developed two methods for estimating the binormal parameters. One of their methods uses a maximum profile likelihood estimator and the other uses a pseudo maximum likelihood estimator. A new robust and efficient semiparametric maximum likelihood method is proposed by Zhou and Lin (2008). Li, Tiwari, and Wells (1999) studied a semiparametric sample quantile comparison between a parametric model for the case group and a nonparametric model for the control population. The authors proved that the semiparametric method has a smaller asymptotic variance.

Qin and Zhang (1997), Qin and Zhang (2003) developed a logistic regression model by assuming a density ratio model for case and control populations and showed that the method was more robust than the parametric model and more efficient than the nonparametric model. For a given biomarker results $T = t$, the logistic model is given by

$$P(D = 1|T = t) = \frac{exp\{\alpha + \beta * r(t)\}}{1 + exp\{\alpha + \beta * r(t)\}}, \tag{1.20}$$

where $r(t)$ is a smooth function of t. Let $f(t)$ and $g(t)$ be the density distribution to $F(t)$ and $G(t)$, respectively. The density ratio is given by

$$\frac{f(t)}{g(t)} = exp\{\alpha^* + \beta * r(t)\}. \tag{1.21}$$

where $\alpha^* = \alpha + log(1 - P(D = 1)/P(D = 1))$. Thus we have biomarker results with density $f(x)$ for cases and biomarker results with density $f(x) = exp\{\alpha^* + \beta * r(x)\}g(x)$ for controls and

the cdfs are given by

$$\hat{F}_{LG}(c) = \frac{1}{m}\sum_{i=1}^{N} \frac{exp\{\alpha + \beta r(T_i)\}I(T_i \leq c)}{1 + \rho exp\{\alpha + \beta r(T_i)\}I(T_i \leq c)}, \tag{1.22}$$

$$\hat{G}_{LG}(c) = \frac{1}{n}\sum_{i=1}^{N} \frac{I(T_i \leq c)}{1 + \rho exp\{\alpha + \beta r(T_i)\}I(T_i \leq c)}, \tag{1.23}$$

where $N = n + m$, $\rho = m/n$ and (α, β) could be estimated by solving the score equations. The ROC curve is estimated by

$$\widehat{ROC}_{LG}(u) = 1 - \hat{F}_{LG}(\hat{G}_{LG}^{-1}(1-u)). \tag{1.24}$$

Wan and Zhang (2007) proposed a smooth semiparametric ROC estimator based on a kernel distribution function estimator in the logistic regression model and showed that it was more efficient than existing nonparametric, parametric and semiparametric binormal estimators. The proposed semiparametric kernel estimators of case and control distributions are given by

$$\hat{F}_{LK}(c) = \frac{1}{m}\sum_{i=1}^{N} \frac{exp\{\alpha + \beta r(T_i)\}}{1 + \rho exp\{\alpha + \beta r(T_i)\}} K\left(\frac{c - T_i}{h}\right), \tag{1.25}$$

$$\hat{G}_{LK}(c) = \frac{1}{n}\sum_{i=1}^{N} \frac{1}{1 + \rho exp\{\alpha + \beta r(T_i)\}} K\left(\frac{c - T_i}{h}\right), \tag{1.26}$$

where h is the kernel bandwidth and $K(t)$ is kernel density estimator.

1.3 Two ROC Curves

Another application of receiver operating characteristic curve is to compare the accuracy of two diagnostic biomarkers to determine if the two biomarkers have the same performance. The ROC

summary measures can be used for the comparison of biomarkers. These measures include the AUC, pAUC and wAUC described in Section 1.2. If the AUCs are the same, the two diagnostic biomarkers may have the same accuracy. But it is possible that the two ROC curves have the same AUC but different shapes.

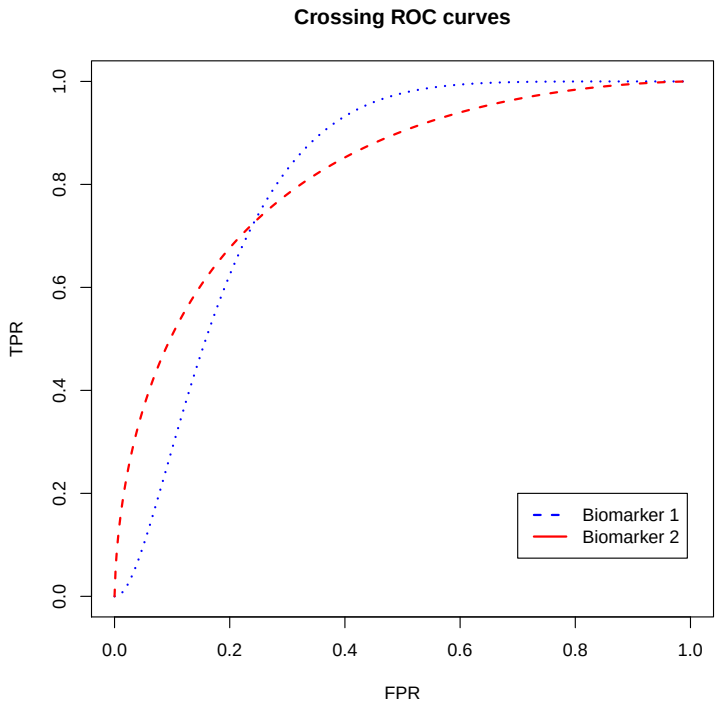

Figure 1.3: Crossing ROC curves

To compare the weighted areas under the two ROC curves, the null and alternative hypotheses are

$$H_0 : wAUC_1 = wAUC_2 \quad v.s. \quad H_1 : wAUC_1 \neq wAUC_2$$

or

$$H_0 : \Delta = 0 \quad v.s. \quad H_1 : \Delta \neq 0,$$

where $wAUC_l$ is the wAUC of the lth ROC curve, and we denote the difference as $\Delta = wAUC_1 - wAUC_2$. The test statistic of the hypotheses follows a normal distribution asymptotically and is

given by

$$Z = \frac{\hat{\Delta}}{\sqrt{var(\hat{\Delta})}} = \frac{\widehat{wAUC}_1 - \widehat{wAUC}_2}{\sqrt{var(\widehat{wAUC}_1 - \widehat{wAUC}_2)}},$$

where the variance of the difference $\hat{\Delta}$ is

$$var(\hat{\Delta}) = var(\widehat{wAUC}_1 - \widehat{wAUC}_2) = var(\widehat{wAUC}_1) + var(\widehat{wAUC}_2) - 2cov(\widehat{wAUC}_1, \widehat{wAUC}_2)$$

and $cov(\widehat{wAUC}_1, \widehat{wAUC}_2)$ is the covariance between $\widehat{wAUC}_1$ and $\widehat{wAUC}_2$, which is zero in an unpaired design setting.

For independent continuous biomarker results, we could compare ROC summary measures using parametric, nonparametric and semiparametric methods. Suppose we have m case subjects, n control subjects and ℓ diagnostic biomarkers, where $\ell = 1, 2$. Denote the biomarker results on case subjects are $T^d_{\ell i}$, where $i = 1, \ldots, m$, which has a distribution $F_\ell(x)$ and biomarker results on control subjects are $T^{\bar{d}}_{\ell j}$, where $j = 1, \ldots, n$, which has a distribution $G_\ell(y)$. For a threshold c, which is a constant in $(-\infty, +\infty)$, we have $S_{D,\ell}(c) = TPR_\ell(c) = 1 - F_\ell(c) = P(T^d_{\ell i} > c)$ and $S_{\bar{D},\ell}(c) = FPR_\ell(c) = 1 - G_\ell = P(T^{\bar{d}}_{\ell i} > c)$. Denote $FPR_\ell = u$, the ℓth ROC curves are given by

$$ROC_\ell(u) = 1 - F_\ell(G_\ell^{-1}(1-u)) = S_{D,\ell}(S^{-1}_{\bar{D},\ell}(u)), \tag{1.27}$$

and the ℓth wAUC is given by

$$wAUC_\ell = \int_0^1 ROC_\ell dW(u). \tag{1.28}$$

When $W(u) = u$, the AUCs are given by

$$AUC_\ell = \int_0^1 ROC_\ell du = P(T^d_{\ell i} > T^{\bar{d}}_{\ell j}). \tag{1.29}$$

1.3.1 Parametric Methods

In a binormal model, the case and control biomarker results of the first biomarker follow normal distributions $N(\mu_{1,D}, \sigma^2_{1,D})$ and $N(\mu_{1,\bar{D}}, \sigma^2_{1,\bar{D}})$,the case and control biomarker results of the second biomarker follow normal distributions $N(\mu_{2,D}, \sigma^2_{2,D})$ and $N(\mu_{2,\bar{D}}, \sigma^2_{2,\bar{D}})$. The ROC curve $ROC_l(u)$ takes the same form as Equation (1.5) and difference of wAUCs is given by

$$\hat{\Delta}_{BN} = \int_0^1 \widehat{ROC}_{1,BN}(u)dW(u) - \int_0^1 \widehat{ROC}_{2,BN}(u)dW(u), \tag{1.30}$$

and the difference of AUCs Δ^A_{BN} can be estimated by,

$$\hat{\Delta}^A_{BN} = \Phi\left(\frac{\hat{a}_1}{\sqrt{1+\hat{b}_1^2}}\right) - \Phi\left(\frac{\hat{a}_2}{\sqrt{1+\hat{b}_2^2}}\right), \tag{1.31}$$

where $\hat{a}_1 = (\hat{\mu}_{1,D} - \hat{\mu}_{1,\bar{D}})/\hat{\sigma}_{1,D}$, $\hat{b}_1 = \hat{\sigma}_{1,\bar{D}}/\hat{\sigma}_{1,D}$ and $\hat{a}_2 = (\hat{\mu}_{2,D} - \hat{\mu}_{2,\bar{D}})/\hat{\sigma}_{2,D}$, $\hat{b}_2 = \hat{\sigma}_{2,\bar{D}}/\hat{\sigma}_{2,D}$. The variance of estimated AUCs can be estimated by

$$var(\widehat{AUC_\ell}) = \hat{f}_\ell^2 var(\hat{a}_\ell) + \hat{g}_\ell^2 var(\hat{b}_\ell) + 2\hat{f}_\ell \hat{g}_\ell cov(\hat{a}_\ell, \hat{b}_\ell), \tag{1.32}$$

where $\hat{f}_\ell = e^{-\hat{a}_\ell^2/\hat{a}_\ell(1+\hat{b}_\ell^2)}/\sqrt{2\pi(1+\hat{b}_\ell^2)}$, $\hat{g}_l = -\hat{a}_\ell\hat{b}_l e^{-\hat{a}_l^2/\hat{a}_\ell(1+\hat{b}_\ell^2)}/\sqrt{2\pi(1+\hat{b}_\ell^2)^3}$, and $var(\hat{a}_\ell) = (n(\hat{a}_\ell^2+2) + 2m\hat{b}_\ell^2)/2mn$, $var(\hat{b}_\ell) = (m+n)\hat{b}_\ell^2/2mn$, $cov(\hat{a}_\ell, \hat{b}_l) = \hat{a}_l\hat{b}_l/2m$.

1.3.2 Nonparametric Methods

Wieand, Gail, James, and James (1989) compared biomarkers based on their wAUCs for paired and unpaired data. The difference of estimated weighted AUCs is estimated by

$$\hat{\Delta}_{EM} = \widehat{wAUC}_{1,WD} - \widehat{wAUC}_{2,WD} = \int_0^1 \widehat{ROC}_{1,EM}(u)dW(u) - \int_0^1 \widehat{ROC}_{2,EM}(u)dW(u)$$
$$= \int_0^1 \hat{S}_{D,1}(\hat{S}^{-1}_{\bar{D},1}(u))dW(u) - \int_0^1 \hat{S}_{D,2}(\hat{S}^{-1}_{\bar{D},2}(u))dW(u), \tag{1.33}$$

where $\hat{S}_{D,\ell}(c) = \frac{1}{m}\sum_{i=1}^{m} I(T^d_{\ell i} > c)$, $\hat{S}_{\bar{D},\ell}(c) = \frac{1}{n}\sum_{j=1}^{n} I(T^{\bar{d}}_{\ell j} > c)$ and $W(u)$ is a probability measure. When $W(u) = u$, the difference of AUCs is given by

$$\hat{\Delta}^A_{EM} = \int_0^1 \widehat{ROC}_{1,EM}(u)du - \int_0^1 \widehat{ROC}_{2,EM}(u)du \tag{1.34}$$

The asymptotic variance of $\hat{\Delta}_{EM}$ is given by $\sigma^2_{\Delta_{EM}} = v_x^{WD}m + v_y^{WD}/n$, where v_x and v_y have the following forms

$$v_x^{WD} = \sum_{l=1}^{2}\left(\int_0^1\int_0^1 S_{D,\ell}\{S^{-1}_{\bar{D},\ell}(s\wedge t)\}dW(s)dW(t) - \left[\int_0^1 S_{D,\ell}\{S^{-1}_{\bar{D},\ell}(s)\}dW(s)\right]^2\right)$$
$$-2\int_0^1\int_0^1\Big[S_D\{S^{-1}_{\bar{D},1}(s), S^{-1}_{\bar{D},2}(t)\} - S_{d,1}\{S^{-1}_{\bar{D},1}(s)\}S_{D,2}\{S^{-1}_{\bar{D},2}(t)\}\Big]dW(s)dW(t), \tag{1.35}$$

$$v_y^{WD} = \sum_{l=1}^{2}\left[\int_0^1\int_0^1 R'_\ell(s)R'_\ell(t)(s\wedge t)dW(s)dW(t) - \left\{\int_0^1 R_\ell(s)sdW(s)\right\}^2\right]$$
$$-2\int_0^1\int_0^1 R'_1(s)R'_2(t)[S_{\bar{D}}\{S^{-1}_{\bar{D},1}(s), S^{-1}_{\bar{D},2}(t)\} - st]dW(s)dW(t), \tag{1.36}$$

with the derivative of $ROC_\ell(u)$, $R'_\ell(u) = S'_{D,\ell}\{S^{-1}_{\bar{D},\ell}(u)\}/S'_{\bar{D},\ell}\{S^{-1}_{\bar{D},\ell}(u)\}$.

A popular nonparametric method to compare two AUCs is the Delong's generalized U-statistics method. DeLong, DeLong, and Clarke-Pearson (DeLong, DeLong, and Clarke-Pearson 1988) used the Mann-Whitney Statistic to estimate the areas under the ROC curves for all biomarkers and take the difference to compare the AUCs, denoted Δ_{DL}-statistic . The difference between AUC estimators is given by

$$\hat{\Delta}_{DL} = \widehat{AUC}_{1,DL} - \widehat{AUC}_{2,DL} = \frac{1}{mn}\sum_{i=1}^{m}\sum_{j=1}^{n}\Psi(T^d_{1i}, T^{\bar{d}}_{1j}) - \frac{1}{mn}\sum_{i=1}^{m}\sum_{j=1}^{n}\Psi(T^d_{2i}, T^{\bar{d}}_{2j}), \quad (1.37)$$

where

$$\Psi(T^d_{\ell i}, T^{\bar{d}}_{\ell j}) = \begin{cases} 1, & T^d_{\ell i} > T^{\bar{d}}_{\ell j} \\ \frac{1}{2}, & T^d_{\ell i} = T^{\bar{d}}_{\ell j} \\ 0, & T^d_{\ell i} < T^{\bar{d}}_{\ell j} \end{cases}, \quad (1.38)$$

and the variance of Δ^A_{DL} is given by $\sigma^2_{\Delta^A_{DL}} = v^{DL}_x/m + v^{DL}_y/n$, where v^{DL}_x and v^{DL}_y are

$$v^{DL}_x = \frac{1}{m-1}\sum_{i=1}^{m}\Bigg\{\left[\frac{1}{n}\sum_{j=1}^{n}\psi(T^d_{1i}, T^{\bar{d}}_{1j}) - \widehat{AUC}_{1,DL}\right]^2 + \left[\frac{1}{n}\sum_{j=1}^{n}\psi(T^d_{2i}, T^{\bar{d}}_{2j}) - \widehat{AUC}_{2,DL}\right]^2$$
$$- 2\left[\frac{1}{n}\sum_{j=1}^{n}\psi(T^d_{1i}, T^{\bar{d}}_{1j}) - \widehat{AUC}_{1,DL}\right]\left[\frac{1}{n}\sum_{j=1}^{n}\psi(T^d_{2i}, T^{\bar{d}}_{2j}) - \widehat{AUC}_{2,DL}\right]\Bigg\}, \quad (1.39)$$

$$v^{DL}_y = \frac{1}{n-1}\sum_{j=1}^{n}\Bigg\{\left[\frac{1}{m}\sum_{i=1}^{m}\psi(T^d_{1i}, T^{\bar{d}}_{1j}) - \widehat{AUC}_{1,DL}\right]^2 + \left[\frac{1}{m}\sum_{i=1}^{m}\psi(T^d_{2i}, T^{\bar{d}}_{2j}) - \widehat{AUC}_{2,DL}\right]^2$$
$$- 2\left[\frac{1}{m}\sum_{i=1}^{m}\psi(T^d_{1i}, T^{\bar{d}}_{1j}) - \widehat{AUC}_{1,DL}\right]\left[\frac{1}{m}\sum_{i=1}^{m}\psi(T^d_{2i}, T^{\bar{d}}_{2j}) - \widehat{AUC}_{2,DL}\right]\Bigg\}. \quad (1.40)$$

Another nonparametric method is the kernel smoothing ROC method proposed by Zou, Hall, and Shapiro (1997) and Lloyd (1998). The distributions of case and control biomarker results could be estimated by kernel smoothing estimators. In order to compare two ROC curves, the kernel estimator of F_ℓ is

$$\hat{F}_{\ell,KN}(c) = \frac{1}{m}\sum_{i=1}^{m} K_{1,\ell}\left(\frac{c - T^d_{\ell,i}}{h_{1,\ell}}\right), \tag{1.41}$$

and the kernel estimator of G_ℓ is

$$\hat{G}_{\ell,KN}(c) = \frac{1}{n}\sum_{j=1}^{n} K_{2,\ell}\left(\frac{c - T^{\bar{d}}_{\ell,j}}{h_{2,\ell}}\right), \tag{1.42}$$

where c is the possible threshold. So the difference of kernel smoothing wAUC estimators is given by

$$\hat{\Delta}_{KN} = \int_0^1 \hat{S}_{D,1,KN}(\hat{S}^{-1}_{\bar{D},1,KN}(u))dW(u) - \int_0^1 \hat{S}_{D,2,KN}(\hat{S}^{-1}_{\bar{D},2,KN}(u))dW(u), \tag{1.43}$$

where $\hat{S}_{D,\ell,KN}(c) = 1 - \hat{F}_{\ell,KN}(c)$ and $\hat{S}_{\bar{D},\ell,KN}(c) = 1 - \hat{G}_{\ell,KN}(c)$. Zou, Hall, and Shapiro (1997) suggested that the variance of AUC estimated by kernel smoothing method is similar to the one based on the Wilcoxon U-statistics since the kernel smoothing does not affect the true variance to the first order of approximation. Lloyd (1998) gave the explicit form for the difference between the variance of the kernel smoothing AUC and the empirical AUC,

$$var(\widehat{AUC}_{KN}) - var(\widehat{AUC}_{MW}) = \frac{1}{mn}\{h^2(n-1)(g^{'}(0)A + h_3) + h^2(m-1)(g^{'}(0)A + k_3)$$
$$- 2h\alpha_1 g(0) + h^2 g^{'}(A - \frac{1}{2})\},$$

where h_3 and k_3 are negative, $h = \sqrt{h_1^2 + h_2^2}$, $g(.)$ is the density function of difference of case and control results and A is the area under ROC curve, and $(\frac{n}{m})^{1/3} \approx \frac{h_2}{h_1}$. The relative difference

between the variance of AUC_{KN} and variance of AUC_{MW} is $O(h^2)$ and Lloyd also showed that the AUC estimated by using the kernel smoothed method has no general advantage over the AUC estimated by the Wilcoxon U-statistic unless h equals to $o(N^1)$ and is much smaller than the optimal bandwidth. However, the explicit form of the covariance between kernel smoothing AUCs is not available.

Other nonparametric methods have been developed. Zhou and Gatsonis (1996) developed a nonparametric comparison method for incomplete paired data based on Delong's method and derive the covariance matrix of AUC estimators. Bandos, Rockette, and Gur (2005) proposed an exact nonparametric procedure to compare the AUC of two ROC curves for paired data by modifying Venkatraman and Begg's permutation test method (Venkatraman and Begg 1996). It assumes the two diagnostic biomarkers are exchangeable within the same subject and requires a transformation of the original data. Braun and Alonzo (2008) developed a sign biomarker to compare AUCs in a paired design setting based on between subjects permutations of the case and control subjects.

1.3.3 Semiparametric Methods

Semiparametric methods include generalized linear model and least square method. Pepe (2000) proposed a semiparametric ROC estimator using a generalized linear model(GLM) binary regression techniques. She developed the binary regression framework to compare two ROC curves. Suppose the parametric ROC curve model has the form

$$ROC_\ell(u) = g\{\sum_{\ell=1}^{2} \boldsymbol{\beta}_l h_\ell(u)\} = g\{\beta_{11} + \beta_{12} h_1^{-1}(u_\ell) + \beta_{21} I + \beta_{22} I h_2^{-1}(u_\ell)\}, \tag{1.44}$$

where g is some special link function, h_ℓ is the basis functions and $\boldsymbol{\beta}_\ell = (\beta_{\ell 1}, \beta_{\ell 2})$ is the unknown parameters, I the indicator variable corresponding to the two biomarkers, $I = 0$ when $\ell = 1$ and $I = 1$ when $\ell = 2$. For the lth biomarker, the indicator variable $U_{\ell ij}$ has been introduced by using all the possible pairs of biomarker results, $U_{\ell ij} = I[T_{\ell i}^d \geq T_{\ell j}^{\bar{d}}]$ Since the ROC curve could be

written as a conditional probability such as,

$$\begin{aligned} P(T_\ell^d > T_\ell^{\bar{d}} | S_{\ell,\bar{D}}(T_\ell^{\bar{d}}) = u) &= P(T_\ell^d > T_\ell^{\bar{d}} | T_\ell^{\bar{d}} = S_{l,\bar{D}}^{-1}(u_\ell)) \\ &= P(T_\ell^d > S_{\ell,\bar{D}}^{-1}(u)) \\ &= S_{\ell,D}(S_{\ell,\bar{D}}^{-1}(u)) \\ &= ROC_\ell(u), \end{aligned}$$

the ROC curve parametric model could be written as a conditional expectation of $U_{\ell ij}$ with the form

$$E(U_{\ell ij} | S_{\ell,\bar{D}}(Y_\ell) = u) = ROC_\ell(u) = g\{\beta_{11} + \beta_{12} h_1^{-1}(u) + \beta_{21} I + \beta_{22} I h_2^{-1}(u)\}, \qquad (1.45)$$

and the parameters $\boldsymbol{\beta}_\ell$ could be estimated by solving

$$\sum_{i=1}^{m} \sum_{j=1}^{n} \frac{U_{\ell ij} - g\{\Sigma_{\ell=1}^2 \boldsymbol{\beta}_\ell h_\ell(u_j)\}}{g\{\Sigma_{\ell=1}^2 \boldsymbol{\beta}_\ell h_\ell(u_j)\}(1 - g\{\Sigma_{\ell=1}^2 \boldsymbol{\beta}_\ell h_\ell(u_j)\})} \frac{\partial g\{\Sigma_{\ell=1}^2 \boldsymbol{\beta}_\ell h_\ell(u_j)\}}{\partial \boldsymbol{\beta}_\ell} = 0.$$

Besides GLM methods, the unknown parameters in binary regression model in Equation (1.44) $ROC_\ell(u) = g\{\sum_{\ell=1}^2 \boldsymbol{\beta}_\ell h_\ell(u)\}$ could also be estimated by the least square methods proposed by **?**). The general least square (LS) estimating procedure is as follows. For $\ell = 1, 2$ biomarkers, we can choose p partition points $u_{\ell,p} = (u_{\ell,1}, \ldots, u_{\ell,p})^T$ within the boundry interval $[0, 1]$. The ℓth empirical ROC curve is

$$\widehat{ROC}_\ell(u_{\ell,p}) = \hat{S}_{D,\ell}(\hat{S}_{\bar{D},\ell}^{-1}(u_{\ell,p})). \qquad (1.46)$$

Let $\tilde{T}_{\ell,p}^{\bar{d}} = g^{-1}(\widehat{ROC}_\ell(u_{\ell,p}))$ and let $\tilde{\boldsymbol{T}}^{\bar{d}} = (\tilde{\boldsymbol{T}}_1^{\bar{d}}, \tilde{\boldsymbol{T}}_2^{\bar{d}})$, where $\tilde{\boldsymbol{T}}_\ell^{\bar{d}} = (\tilde{T}_{\ell,1}^{\bar{d}}, \ldots, \tilde{T}_{\ell,p}^{\bar{d}})^T$. Let the

design matrix M be

$$M = \begin{pmatrix} M_1 & O \\ M_2 & M_2 \end{pmatrix},$$

where

$$M_1 = \begin{pmatrix} 1 & \dots & 1 \\ g^{-1}(u_{1,1}) & \dots & g^{-1}(u_{1,p}) \end{pmatrix}^T,$$

$$M_2 = \begin{pmatrix} 1 & \dots & 1 \\ g^{-1}(u_{2,1}) & \dots & g^{-1}(u_{2,p}) \end{pmatrix}^T,$$

and O is a $P \times 2$ matrix whose elements are all 0. We get the linear regression equation $\tilde{\boldsymbol{T}} = M\theta + \epsilon$. The least square estimator $\hat{\boldsymbol{\beta}}_{LS} = (M^T M)^{-1} M^T \tilde{\boldsymbol{T}}$ and Tang and Zhou (2009) derived the asymptotic results for the least square method for multivariate ROC models.

In the comparison of two AUCs setting, the GLM method and the LS method have similar forms but different estimation equation. The ROC curve has the form in Equation (1.44). The corresponding wAUC is

$$\widehat{wAUC}_{\ell,SM} = \int_0^1 \widehat{ROC}_{\ell,SM}(u) dW(u), \tag{1.47}$$

and the difference between wAUCs is estimated by

$$\begin{aligned} \hat{\Delta}_{SM} &= \widehat{wAUC}_1 - \widehat{wAUC}_2 \\ &= \int_0^1 g\{\hat{\beta}_{11} + \hat{\beta}_{12} h_1^{-1}(u)\} dW(u) - \int_0^1 g\{\hat{\beta}_{11} + \hat{\beta}_{12} h_\ell^{-1}(u) + \hat{\beta}_{21} + \hat{\beta}_{22} h_2^{-1}(u)\} dW(u). \end{aligned} \tag{1.48}$$

Under the binormal assumption, the ROC curve takes the form

$$\widehat{ROC}_{\ell,SB}(u) = \Phi\{\hat{\beta}_{11} + \hat{\beta}_{12}\Phi^{-1}(u) + \hat{\beta}_{21}I + \hat{\beta}_{22}I\Phi^{-1}(u)\}, \tag{1.49}$$

where $I = 0$ when $\ell = 1$ and $I = 1$ when $\ell = 2$. The AUC difference estimator is

$$\begin{aligned}\hat{\Delta}_{SB} &= \int_0^1 \Phi\{\hat{\beta}_{11} + \hat{\beta}_{12}\Phi^{-1}(u)\}du - \int_0^1 \Phi\{\hat{\beta}_{11} + \hat{\beta}_{12}\Phi^{-1}(u) + \hat{\beta}_{21} + \hat{\beta}_{22}\Phi^{-1}(u)\}du \\ &= \Phi\left(\frac{\hat{\beta}_{11}}{\sqrt{1+\hat{\beta}_{12}^2}}\right) - \Phi\left(\frac{\hat{\beta}_{11}+\hat{\beta}_{21}}{\sqrt{1+(\hat{\beta}_{12}+\hat{\beta}_{22})^2}}\right),\end{aligned} \tag{1.50}$$

1.4 Covariate Adjusted ROC Curves

In previous sections, we have discussed estimation of one ROC curve and comparison of two ROC curves. In this section, we introduce covariate adjusted ROC curves. The patient covariates, such as age, gender, disease history, severity of disease, etc., could affect the accuracy of a diagnostic biomarker. Hence, we need to accommodate patient covariates to account for the covariate effects. In recent years, many regression models have been developed to study the covariate effects on the accuracy of a diagnostic biomarker. We introduce two regression models, including indirect regression models and direct regression models, to study the covariate effects on ROC curves. Under the location-scale family assumption, the indirect regression model fits a regression model for the distribution of biomarker results using disease status and covariates of the patient. The distributions of the biomarker results from diseased patients and nondiseased patients are estimated as functions of covariates so that the covariate effects can be assessed on the ROC curves. The direct regression model fits one regression model directly from all the biomarker results. The baseline function and link function need to be specified and estimated. These two methods can be used for both discrete and continuous covariates and the estimated ROC curves are called covariate adjusted ROC curves.

1.4.1 Indirect ROC Regression Methods

Tosteson and Begg (1988) proposed an indirect regression method to adjust for the covariates. The covariate effects on $S_{1,x}(c)$ and $S_{0,x}(c)$ is modeled first and then the covariate effects on ROC curve is derived. The biomarker result T can be express in the following linear regression model

$$T = \mu(D, X; \beta) + \sigma(D, X; \alpha)\epsilon, \tag{1.51}$$

where ϵ is the residual term with mean 0 and variance 1 with distribution $G_0(.)$. The vectors of location and scale parameters α and β represent the effects of disease status and covariates on the mean and variance of T. It can be shown that $S_{d,x}(c) = G_0(\frac{c-\mu(d,x;\beta)}{\sigma(d,x;\alpha)})$. Let $S_\epsilon = 1 - G_0$ be the survival function of ϵ, hence, the ROC curve is given by

$$ROC_x(u) = S_\epsilon(b(x;\alpha)S_\epsilon^{-1}(u) - a(x;\beta,\alpha)), \tag{1.52}$$

where $S_\epsilon^{-1}(.)$ is the inverse function of $S_\epsilon(.)$, $a(x;\beta,\alpha) = \frac{\mu(d,x;\beta)-\mu(d,x;\beta)}{\sigma(d,x;\alpha)}$, and $b(x;\alpha) = \frac{\sigma(d,x;\alpha)}{\sigma(d,x;\alpha)}$.

Consider an example with $X = x_1$ and $D = d$ to illustrate how the covariate works on the ROC curve. We have $\mu(d, x_1; \beta) = \beta_0 + \beta_1 d + \beta_2 x_1 + \beta_3(d \times x_1)$, where $d = 1, 2$. The variance $\sigma^2(d, x; \alpha)$ does not depend on covariate, therefore it can be written as $\sigma^2(d, x_1; \alpha) = \sigma^2(d)$. The parameters $a(x;\beta,\alpha)$ and $b(x;\alpha)$ are written as $a(x_1;\beta,\alpha) = (\beta_1 + \beta_3 x_1)/\sigma(1)$ and $b(x_1;\alpha) = \sigma(0)/\sigma(1)$. The ROC curve with covariate $X = x_1$ is given by

$$ROC_{x_1}(u) = S_\epsilon(\frac{\sigma(0)}{\sigma(1)}S_\epsilon^{-1}(u) - \frac{\beta_1 + \beta_3 x_1}{\sigma(1)}).$$

With the discrete covariate $x_1 = 0, 1, 2$, we have three covariate adjusted ROC curves.

$$ROC_{x_1=0}(u) = S_\epsilon(\frac{\sigma(0)}{\sigma(1)}S_\epsilon^{-1}(u) - \frac{\beta_1}{\sigma(1)}),$$

$$ROC_{x_1=1}(u) = S_\epsilon(\frac{\sigma(0)}{\sigma(1)} S_\epsilon^{-1}(u) - \frac{\beta_1 + \beta_3}{\sigma(1)}),$$

$$ROC_{x_1=2}(u) = S_\epsilon(\frac{\sigma(0)}{\sigma(1)} S_\epsilon^{-1}(u) - \frac{\beta_1 + 2\beta_3}{\sigma(1)}).$$

To estimate the ROC curve, Zhou, Mcclish, and Obuchowski (2002) introduced a two-stage procedure. The generalized estimating equations (GEE) method is first used to estimate location and scale parameters β and α based on the mean and variance of the biomarker results. Then the residuals are used to estimate the baseline function S_ϵ and $ROC_x(u)$. In the situation that G_0 is the standard normal distribution, the AUC has an explicit form,

$$\widehat{AUC}_x = \Phi(\frac{a(x; \hat{\beta}, \hat{\alpha})}{\sqrt{1 + (b(x; \hat{\alpha}))^2}}). \tag{1.53}$$

The AUC for ROC curve with covariate $X = x_1$ is given by

$$\widehat{AUC}_{x_1} = \Phi(\frac{a(_1; \hat{\beta}, \hat{\alpha})}{\sqrt{1 + (b(_1; \hat{\alpha}))^2}}).$$

When the discrete covariate $x_1 = 0, 1, 2$, the AUCs are

$$\widehat{AUC}_{x_1=0} = \Phi(\frac{a(0; \hat{\beta}, \hat{\alpha})}{\sqrt{1 + (b(0; \hat{\alpha}))^2}}),$$

$$\widehat{AUC}_{x_1=1} = \Phi(\frac{a(1; \hat{\beta}, \hat{\alpha})}{\sqrt{1 + (b(1; \hat{\alpha}))^2}}),$$

$$\widehat{AUC}_{x_1=2} = \Phi(\frac{a(2; \hat{\beta}, \hat{\alpha})}{\sqrt{1 + (b(2; \hat{\alpha}))^2}}).$$

1.4.2 Direct ROC Regression Methods

Zhou, Mcclish, and Obuchowski (2002) pointed out that, it is difficult to interpret the regression parameters on the ROC curve estimated by the indirect regression model. Pepe (1997) proposed the direct regression method which models the covariate effects on the ROC curve, and parametric distributions for the biomarker results may or may not be needed. Let $X_{\bar{D}}$ be a vector of common covariates to all the patients, and let X_D be a vector of covariates to diseased patients. Denote $X = (X_{\bar{D}}, X_D)$ as the vector of all the covariates. Let T_1 and T_0 be the abnormal and normal biomarker results; let $S_{1,z}$ and $S_{0,z}$ be the survival function of T_1 and T_0 given covariates $X = x$. The corresponding distributions of T_1 and T_0 given covariates $X = x$ are $F_{1,x}$ and $F_{0,x}$ The ROC curve associated with $x = (x_{\bar{D}}, x_D)$ is given by

$$ROC_x(u) = S_{1,x}(S_{0,x}^{-1}(u)). \tag{1.54}$$

The covariates effect on ROC curve can be modeled by the following equation,

$$ROC_x(u) = g\{H(u) + \beta x\}, \tag{1.55}$$

where $g(.)$ is the link function; $H(u)$ is a baseline monotone increasing function of u; $\beta \boldsymbol{X}$ is a linear regression model which summarize the effect of the patient covariates $\boldsymbol{X}$. Note that, when $g(.) = \Phi(.)$ and $H(.) = \alpha_0 + \alpha_1 \Phi^{-1}(.)$, the model (1.55) becomes binormal model.

Zhou, Mcclish, and Obuchowski (2002) claimed that not only the direct regression method models the effect of patient covariates directly, it is also more robust than indirect regression method which makes assumptions on the distribution of biomarker results. Pepe (1998) showed that the direct regression method allows a broader range of settings and can include interactions between false positive rates and covariates. Also the direct regression model method enables comparing ROC curves for tests with different scales for diseased and nondiseased populations.

To estimate the parameters of the direct regression model, Pepe (1997) proposed a two steps algorithm. Denote the abnormal result as $T_{1i}, i = 1, \ldots, n_1$ and normal result as $T_{0j}, j = 1, \ldots, n_0$.

First step is to estimate $S_{0,x}(u)$ by using likelihood-based score equations if the data are independent, or using generalized estimating equations if data are not independent. The second step is to estimate the baseline link function $H(u)$ and parameters β by minimizing the following function

$$\sum_{(i:D_i=1)} \int_0^1 w(u)[I\{T_i \geq S_{0,x}^{-1}(u)\} - g\{H(u) + \beta x\}]^2 du, \tag{1.56}$$

where $w(u)$ is a weight function. Cai and Pepe (2002) extended the direct regression models to allow nonparametric baseline functions. This semiparametric approach has two steps. For the first step, define a survival function $S_0(c) = \frac{1}{n_D} \sum_{j=1}^{n_D} I(T_{0j} - \gamma x > c)$, where γ is the solution to $\sum_{j=1}^{n_D} I(T_{0j} - \gamma x) = 0$, and then estimate $S_{0,x}(u)$ by equation $S_{0,x}(c) = S_0(c - \gamma x)$. For the second step, define $S_{0,x}(c)^{-1} = S_0^{-1}(c) + \gamma x$, then estimate baseline function $H(u)$ and parameters β by solving the same equations in Pepe's paper (Pepe 1997).

Pepe (2000) and Dodd (2001) proposed a generalized linear model method to estimate the ROC curve and AUC with covariates, which is easier to solve the estimating equations by standard software. First, introduce the indicator variable $U_{ij} = I[T_{1i} \geq T_{0j}]$, which contains all the possible pairs of the biomarker results. The parameters are estimated by solving

$$\sum_{i=1}^{n_1} \sum_{j=1}^{n_0} \frac{U_{ij} - g\{\beta x + h(u_j)\}}{g\{\beta x + h(u_j)\}(1 - g\{\beta x + h(u_j)\})} \frac{\partial g\{\beta x + h(u_j)\}}{\partial \beta} = 0. \tag{1.57}$$

The AUC is given by $AUC_x = E(U_{ij}|X = x) = P(T_{1i} \geq T_{0j}|X = x)$. Alonzo and Pepe (2002) consider the indicator variable of the form $U_{ij} = I[T_{1i} \geq S_{0,x}^{-1}(u)]$. They estimate $S_{0,x}^{-1}(u)$ by using empirical estimates and then solve the same equations as in Pepe's paper (Pepe 2000).

1.5 Clustered ROC Data

In clustered ROC data, each subject is a cluster, which contains both case and control biomarker results. The cluster size could be fixed or informative. To estimate the ROC curve, the within cluster correlation should be considered. Obuchowski (1997) proposed a nonparametric method using Wilcoxon-Mann-Whitney U statistics, is also an expansion of Delong's nonparametric methods to the clustered ROC data. Let T_{ij}^{d} denote the jth continuous case biomarker result in ith cluster, where $i = 1, \ldots, I$ and $j = 1, \ldots, m_i$ and $T_{ik}^{\bar{d}}$ denotes the kth continuous control biomarker result in ith cluster, where $k = 1, \ldots, n_i$. The total number of case biomarker results in all clusters is $M = \sum_{i=1}^{I} m_i$ and the total number of control biomarker results in all clusters is $N = \sum_{i=1}^{I} n_i$. So the estimated estimated AUC for clustered ROC data was given by

$$\widehat{AUC}_{OB} = \frac{1}{MN} \sum_{i=1}^{I} \sum_{i'=1}^{I} \sum_{j=1}^{m_i} \sum_{k=1}^{n_{i'}} \psi(T_{ij}^{d}, T_{i'k}^{\bar{d}}), \tag{1.58}$$

where

$$\psi(T_{ij}^{d}, T_{i'k}^{\bar{d}}) = \begin{cases} 1, & T_{ij}^{d} > T_{i'k}^{\bar{d}} \\ \frac{1}{2}, & T_{ij}^{d} = T_{i'k}^{\bar{d}} \\ 0, & T_{ij}^{d} < T_{i'k}^{\bar{d}} \end{cases}, \tag{1.59}$$

In order to estimate the variance of $\widehat{AUC}_{OB}$, first we can transform the case and control biomarker results into X-components and Y-components, which are

$$V_{10}(T_{ij}^{d}) = \frac{1}{M} \sum_{i'=1}^{I} \sum_{k=1}^{n_{i'}} \psi(T_{ij}^{d}, T_{i'k}^{\bar{d}}),$$

for all T_{ij}^{d} and

$$V_{01}(T_{i'k}^{\bar{d}}) = \frac{1}{N}\sum_{i=1}^{I}\sum_{j=1}^{m_i}\psi(T_{ij}^{d}, T_{i'k}^{\bar{d}}),$$

for all $T_{i'k}^{\bar{d}}$. Then let $V_{10}(T_{i.}^{d})$ and $V_{01}(Y_{i.})$ be the sum of the X-components and Y-components for the ith cluster, and let S_{10} and S_{01} be the sum of squares of the T^{d}-components and $T^{\bar{d}}$-components, which are given by

$$S_{10} = \frac{I}{(I-1)N}\sum_{i=1}^{I}[V_{10}(T_{i.}^{d}) - m_i\widehat{AUC}_{OB}],$$

and

$$S_{01} = \frac{I}{(I-1)M}\sum_{i=1}^{I}[V_{01}(T_{i.}^{\bar{d}}) - n_i\widehat{AUC}_{OB}].$$

In order to take into account the correlation between case and control observations with in the same cluster, they introduced

$$S_{11} = \frac{I}{I-1}\sum_{i=1}^{I}([V_{10}(T_{i.}^{d}) - m_i\widehat{AUC}_{OB}][V_{01}(T_{i.}^{\bar{d}}) - n_i\widehat{AUC}_{OB}]).$$

So that the variance of estimated AUC is estimated by

$$\widehat{var}(\widehat{AUC}_{OB}) = \frac{1}{M}S_{10} + \frac{1}{N}S_{01} + \frac{2}{MN}S_{11}, \tag{1.60}$$

and $(\widehat{AUC}_{OB} - AUC_{OB})/\sqrt{\widehat{var}(\widehat{AUC}_{OB})}$ is asymptotically $N(0,1)$. The author also proposed the covariance of two estimated AUCs for comparing two ROC curves. Denote $\widehat{AUC}_{1,OB}$ and

$\widehat{AUC}_{2,OB}$ as the estimated area under the two ROC curves and define

$$S_{10}^{1,2} = \frac{I}{(I-1)M}\sum_{i=1}^{I}([V_{10}^{1}(T_{i.}^{d}) - m_i\widehat{AUC}_{1,OB}][V_{10}^{2}(T_{i.}^{d}) - m_i\widehat{AUC}_{2,OB}]),$$

$$S_{01}^{1,2} = \frac{I}{(I-1)N}\sum_{i=1}^{I}([V_{01}^{1}(T_{i.}^{\bar{d}}) - n_i\widehat{AUC}_{1,OB}][V_{01}^{2}(T_{i.}^{\bar{d}}) - n_i\widehat{AUC}_{2,OB}]),$$

$$S_{11}^{1,2} = \frac{I}{I-1}\sum_{i=1}^{I}([V_{10}^{1}(T_{i.}^{d}) - m_i\widehat{AUC}_{1,OB}][V_{01}^{2}(T_{i.}^{\bar{d}}) - n_i\widehat{AUC}_{2,OB}]),$$

and

$$S_{11}^{2,1} = \frac{I}{I-1}\sum_{i=1}^{I}([V_{10}^{2}(T_{i.}^{d}) - m_i\widehat{AUC}_{2,OB}][V_{01}^{1}(T_{i.}^{\bar{d}}) - n_i\widehat{AUC}_{1,OB}]),$$

where $V_{10}^{\ell}(T_{i.}^{d})$ and $V_{01}^{\ell}(T_{i.}^{\bar{d}})$ be the sum of the X-components and Y-components for the ith cluster from the lth ROC curve. So thje estimated covariance between the areas under two ROC curve is

$$\widehat{cov}(\widehat{AUC}_{1,OB}, \widehat{AUC}_{2,OB}) = \frac{S_{10}^{1,2}}{M} + \frac{S_{01}^{1,2}}{N} + \frac{S_{11}^{1,2}}{MN} + \frac{S_{11}^{2,1}}{MN}, \tag{1.61}$$

Li and Zhou (2008) proposed a unified approach to nonparametric comparisons of ROC curves for clustered data. Let $X_{\ell ij}$ denote the jth continuous case biomarker result of ℓth marker in ith cluster,which has distribution F_ℓ , where $i = 1, \ldots, I$, $\ell = 1, 2$ and $j = 1, \ldots, m_{\ell i}$ and Y_{lik} denotes the kth continuous control biomarker result of ℓth marker in ith cluster, which has distribution G_ℓ, where $k = 1, \ldots, n_{\ell i}$. The total number of case results in all clusters is $M_\ell = \sum_{i=1}^{I} m_{\ell i}$ and the total number of control results in all clusters is $N_\ell = \sum_{i=1}^{I} n_{\ell i}$. So the empirical ROC curve is defined by

$$\widehat{ROC}_{\ell,LZ}(u) = 1 - \hat{F}_{l,EM}(\hat{G}_{\ell,EM}^{-1}(1-u)), \tag{1.62}$$

where $\hat{F}_{\ell,EM}(c) = \sum_{i=1}^{I}\sum_{j=1}^{m_{\ell i}} I(X_{\ell ij} \le c)/N_\ell$ and $\hat{G}_{\ell,EM}(c) = \sum_{i=1}^{I}\sum_{k=1}^{n_{\ell i}} I(Y_{\ell ik} \le c)/M_\ell$. Assume that as $I \to \infty$, $I^{-1}\sum_{i=1}^{\ell} n_{\ell i}^v \to \lambda_{\ell v}$, and $I^{-1}\sum_{i=1}^{I} m_{\ell i}^v \to \gamma_{\ell v}$ for some positive constants $\lambda_{\ell v}$ and $\gamma_{\ell v}$, $\ell = 1, 2$ and $v = 1, 2, 3$. Then

$$\sqrt{n}\begin{pmatrix} \hat{F}_{1,EM}(c) - F_{1,EM}(c) \\ \hat{F}_{2,EM}(c) - F_{2,EM}(c) \\ \hat{G}_{1,EM}(c) - G_{1,EM}(c) \\ \hat{G}_{2,EM}(c) - G_{2,EM}(c) \end{pmatrix} \to \begin{pmatrix} W_{F_{1,EM}}(c) \\ W_{F_{2,EM}}(c) \\ W_{G_{1,EM}}(c) \\ W_{G_{2,EM}}(c) \end{pmatrix} \quad as \quad n \to \infty,$$

where $(W_{F_{1,EM}}(c), W_{F_{2,EM}}(c), W_{G_{1,EM}}(c), W_{G_{2,EM}}(c))'$ is a Gaussian processes vector with mean 0. Then assume $F_{1,EM}$ and $G_{1,EM}$ have derivatives $F'_{1,EM}$ and $G'_{1,EM}$. Then the joint limiting distribution of $(\widehat{ROC}_{1,LZ}(u), \widehat{ROC}_{2,LZ}(u))$ is given by, as $n \to \infty$,

$$\sqrt{n}\begin{pmatrix} \widehat{ROC}_{1,LZ}(u) \\ \widehat{ROC}_{2,LZ}(u) \end{pmatrix} \to \begin{pmatrix} Z_1(1-u) \\ Z_2(1-u) \end{pmatrix} \quad as \quad n \to \infty,$$

where

$$Z_{\ell,LZ}(u) = -\frac{G'_{\ell,EM}(F^{-1}_{\ell,EM}(u))}{F'_{\ell,EM}(F^{-1}_{\ell,EM}(u))} W_{F_{\ell,EM}}(F^{-1}_{\ell,EM}(u))) + W_{G_{\ell,EM}}(F^{-1}_{\ell,EM}(u))).$$

To compare the area under two ROC curves, let $D_{LZ}(u) = ROC_{1,LZ}(u) - ROC_{2,LZ}(u)$. Then as $n \to \infty$,

$$\sqrt{n}(\hat{D}_{LZ}(u) - D_{LZ}(u)) \to V(u) = Z_{2,LZ}(1-u) - Z_{1,LZ}(1-u),$$

where $V(u)$ is the limiting process. Thus the difference between the AUCs could be estimated by

weighted areas under two ROC curves

$$\hat{\Delta}_{LZ} = \int_0^1 \hat{D}_{LZ}(u) dW(u). \tag{1.63}$$

1.6 Resampling Methods on Clustered Data

Marginal approaches have been developed for clustered data. Liang and Zeger (1986) and Zeger and Liang (1986) proposed a class of generalized estimating equations (GEE) methods to handle the dependent repeated data type, and they used the GEE methods on longitudinal data analysis. However, their method may not work well for if the clustered binary data has different correlation structure and informative cluster size, which occurs when the cluster size is affected by the outcome. Hoffman, Sen, and Weinberg (2001) proposed within cluster resampling (WCR) methods for clustered binary data. They have showed that WCR method worked well with different within cluster correlations and eliminate the effect of informative cluster size. Follmann, Proschan, and Leifer (2003) developed the within cluster resampling method and applied the method to angular data, Bayesian inference, genetics data and data with random cluster sizes. Denote the observation X_{ij} as the jth observation for cluster i, where $i = 1, \ldots, I$ and $j = 1, \ldots, m_i$. So the ensemble of original data could be written as a row vector

$$\mathbf{X} = (X_{11}, \ldots, X_{1m_1}, X_{21}, \ldots, X_{2m_2}, \ldots, X_{I1}, \ldots, X_{Im_I}).$$

One observation is randomly selected from each cluster and the new resampled data has I independent observations. For the qth resampling, let the random selected observation from ith cluster be X^*_{qi}, the qth resampled independent dataset is $\mathbf{X}^*_q = \{X^*_{q1}, X^*_{q2}, \ldots, X^*_{qI}\}$.

Hoffman, Sen, and Weinberg (2001) proposed the WCR estimator for GLM model. The generalized linear model is fitted by the qth resampled dataset $\mathbf{X}^*_q$. The qth resampled model parameter is $\hat{\beta}_q$, where $q = 1, \ldots, Q$ and the process is repeated Q times. Thus the within cluster resampling

estimator is given by

$$\bar{\beta}_Q = \frac{1}{Q}\sum_{q=1}^{Q}\hat{\beta}_q. \tag{1.64}$$

Follmann, Proschan, and Leifer (2003) applied the WCR to other settings. Let $\hat{\beta}_q = \hat{\beta}\{\mathbf{X}_q^*\}$ be the qth estimator obtained by any statistical function or procedure $\mathcal{P}$ using the qth resampled dataset $\mathbf{X}_q^*$. The major steps are given in Table 1.1 and the variance of $\bar{\beta}_Q$ is given by

Table 1.1: Schematic representation of WCR method

	$\mathbf{X}$				
	$\downarrow$				
1	$\mathbf{X}_1^*$	$\rightarrow$	$\mathcal{P}$	$\rightarrow$	$\hat{\beta}_1, \hat{\sigma}_1^2$
2	$\mathbf{X}_2^*$	$\rightarrow$	$\mathcal{P}$	$\rightarrow$	$\hat{\beta}_2, \hat{\sigma}_2^2$
$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$
Q	$\mathbf{X}_Q^*$	$\rightarrow$	$\mathcal{P}$	$\rightarrow$	$\hat{\beta}_Q, \hat{\sigma}_Q^2$
					$\Downarrow$
					$\bar{\beta}_Q, \bar{\sigma}_Q^2, S_{\hat{\beta}}^2$

$$\widehat{var}(\bar{\beta}_Q) = \frac{\sum_{q=1}^{Q}\hat{\sigma}_q^2}{Q} - \frac{\sum_{q=1}^{Q}(\hat{\beta}_q - \bar{\beta}_Q)^2}{Q-1} = \bar{\sigma}_Q^2 - S_{\hat{\beta}}^2$$

Williamson, Datta, and Satten (2003) proposed the cluster weighted generalized estimating equation method (CWGEE) to simplify the WCR for GEE the method under the informative cluster size situation. The CWGEE method is to solve

$$\mathcal{U}(\beta) = \sum_{i=1}^{I}\frac{1}{m_i}\sum_{j=1}^{m_i}\mathbf{U}_{ij}(\beta) = 0, \tag{1.65}$$

to estimate the parameter β, where $\mathbf{U}_i(\beta)$ is an estimating function to be used in the ith cluster and $E\{\mathbf{U}_I(\beta)\} = 0$ under the true marginal parameter β for marginal model. Denote the solution to

$\mathcal{U}(\beta) = 0$ as $\hat{\beta}_{CWGEE}$ and define $\hat{\beta}_{WCR} = \lim_{Q\to\infty} \bar{\beta}_Q$, they showed that

$$\hat{\beta}_{WCR} - \hat{\beta}_{CWGEE} \to 0.$$

They also showed the asymptotic distribution of CWGEE estimator

$$\sqrt{I}(\hat{\beta}_{CWGEE} - \beta) \to N(0, \hat{\Sigma}_{CWGEE}),$$

where

$$\hat{\Sigma}_{CWGEE} = \hat{H}^{-1}\hat{V}\hat{H}^{-1},$$

$$\hat{H} = I^{-1}\sum_{i=1}^{I}\frac{1}{m_i}\sum_{j=1}^{m_i}\left.\frac{\partial \mathbf{U}_{ij}(\beta)}{\partial\beta}\right|_{\beta=\hat{\beta}_{CWGEE}},$$

and

$$\hat{V} = I^{-1}\sum_{i=1}^{I}\{\frac{1}{m_i}\sum_{j=1}^{m_i}\mathbf{U}_{ij}(\hat{\beta}_{CWGEE})\}\{\frac{1}{m_i}\sum_{j=1}^{m_i}\mathbf{U}_{ij}(\hat{\beta}_{CWGEE})\}^T.$$

The CWGEE method only needs to solve a single weighted score function and It avoids the computationally intensive resampling required in the WCR method, while achieving similar results.

Datta and Satten (2005) proposed a rank sum test for two sample clustered data motivated by Hoffman, Sen, and Weinberg (2001) and Williamson, Datta, and Satten (2003). They simplified the WCR method and derived explicit form for their rank sum test under hypothesis $F = G$. Denote g_{ij} as the group membership of the jth observation in ith cluster and $n_{i1} = \sum_{j=1}^{m_i} g_{ij}$. For the qth resampling, assume that the randomly selected observation from ith cluster is X^*_{qi}, the rank of X^*_{qi} among the resampled data is R_{qi} the group membership is g_{qi}. Since the resampled data are independent, the qth Wilcoxon rank sum statistic is given by

$$W_q = \frac{1}{I+1}\sum_{i=1}^{I} g_{qi}R_{qi}. \tag{1.66}$$

Then average W_q over all possible choice of qth resampled data $\mathbf{X}_q^*$ given the original data and conduct a Z test statistic, which is

$$Z = \frac{S - E(S)}{\sqrt{v\hat{a}r(S)}}, \tag{1.67}$$

where

$$S = E(W_q|\mathbf{X}) = \frac{1}{I+1}\sum_{i=1}^{I}\sum_{j=1}^{m_i}\frac{g_{ij}}{m_i}[1 + \frac{1}{2}\sum_{i\neq k}\{F_k(X_{ij}) + F_k(X_{ij-})\}],$$

with

$$F_i(x) = \frac{1}{n_i}\sum_{j=1}^{m_i} I[X_{ij} < x].$$

Then they got

$$E(S) = E(E(W_R|(\mathbf{X}, \mathbf{g})) = E(E(W_R|\mathbf{g})) = E(\frac{1}{2}\sum_{i=1}^{I} g(i)) = \frac{1}{2}\sum_{i=1}^{I}\frac{n_{i1}}{n_i}. \tag{1.68}$$

The variance of S is given by

$$v\hat{a}r(S) = \sum_{i=1}^{I}\{\hat{W}_i - E(W_i)\}^2, \tag{1.69}$$

where

$$\hat{W}_i = \frac{1}{2n_i(I+1)}\sum_{j=1}^{m_i}\left\{\{(I-1)g_{ij} - \sum_{k\neq i}^{I}\frac{n_{k1}}{n_k}\}\{F(X_{ij}) + F(X_{ij-})\}\right\},$$

and

$$E(\hat{W}_i) = \frac{1}{2(I-1)}\left((I-1)\frac{n_{i1}}{n_i} - \sum_{k\neq i}^{I}\frac{n_{i1}}{n_i}\right)$$

$$= \frac{I}{2(I-1)}\left(\frac{n_{i1}}{n_i} - \frac{1}{M}\sum_{k=1}^{I}\frac{n_{i1}}{n_i}\right).$$

The asymptotic distribution is given by

$$\frac{S - E(S)}{\sqrt{\hat{var}(S)}} \to N(0,1), \text{ as } M \to \infty,$$

under the two conditions

$$\sum_{i=1}^{I}(n_i/\sum_{i=1}^{I} n_i)^2 \to 0, \text{ as } M \to \infty,$$

and

$$\liminf_{I\to\infty} \frac{1}{I}\sum_{i=1}^{I} var(W_i) > 0.$$

1.7 Organization of the Dissertation

In Chapter 2, we first introduce the WCR methods for clustered ROC data to evaluate one ROC curve. We derive the WCR estimating rules to estimate the AUC and the corresponding variance. We compare the proposed methods with the Obuchowski's method and the traditional parametric and nonparametric methods through extensive simulation studies. We illustrate the proposed methods through two data examples. In Chapter 3, we introduce the WCR methods to compare two ROC curves for clustered ROC data. We compare the proposed methods with the Obuchowski's method and the traditional parametric and nonparametric methods through extensive simulation studies. In chapter 4, we introduce the WCR methods on estimating the covariate adjusted ROC curves and

compare the proposed methods with the tradition methods through extensive simulation studies. In Appendix A, we describe the data used in section 2. In Appendix B, we list the R functions and packages used for our simulation studies. Appendix C displays the simulation settings which we used to generate the datasets.

1.8 Contribution of the Dissertation

The major contribution of this dissertation is that it provides a patient level estimator from resampled data sets for clustered ROC data. The proposed methods use one resampled observation to represent a patient's status. The traditional methods use one observation to represent the disease status of a location from the patient. Hence, the ROC curve estimated by the proposed methods is to determine how well a biomarker test works on distinguishing the diseased patient from nondiseased patient.

Also, the WCR methods provide a general framework on estimating the ROC curves for clustered ROC data. We can estimate the ROC curves, as well as the corresponding ROC measures including the AUC, the partial AUC and the TPR at a fixed FPR. We can also choose from the parametric WCR, the nonparametric WCR and the semiparametric WCR methods according to the data type and distribution assumptions.

Chapter 2: Within Cluster Resampling (WCR) Methods for One ROC Curve

2.1 Evaluating One Biomarker

We propose within cluster resampling methods for cluster ROC data. Let T_{ij}^{d} denote the jth continuous diseased result in the ith cluster, where $i = 1, \ldots, I$, $j = 1, \ldots, m_i$, and $T_{ij}^{d} \sim F$. Let $T_{ik}^{\bar{d}}$ denotes the kth continuous nondiseased result in the ith cluster, where $k = 1, \ldots, n_i$, and $T_{ik}^{\bar{d}} \sim G$. The total number of diseased biomarker results in all clusters is $M = \sum_{i=1}^{I} m_i$ and the total number of nondiseased biomarker results in all clusters is $N = \sum_{i=1}^{I} n_i$. For each cluster, there are diseased and nondiseased biomarker results. The informative cluster size is $n_i + m_i$ which is the number of observations in the ith cluster. Hence the ensemble of data is denoted by a long vector

$$(\mathbf{T^{d}}, \mathbf{T^{\bar{d}}}) = (T_{11}^{d}, \ldots, T_{1n_1}^{d}, T_{11}^{\bar{d}}, \ldots, T_{1m_1}^{\bar{d}}, \ldots, T_{I1}^{d}, \ldots, T_{In_I}^{d}, T_{I1}^{\bar{d}}, \ldots, T_{Im_I}^{\bar{d}}).$$

The resampling process is similarly carried out as that in Hoffman, Sen, and Weinberg (2001) and Follmann, Proschan, and Leifer (2003). For the qth resample, $q = 1, \ldots, Q$, we randomly select one biomarker result out of $n_i + m_i$ from the ith cluster, and denote the selected observation $T_{i,q}^{*}$, which could either be a diseased or nondiseased biomarker results. And to develop some notation, we rearrange the resampled $T_{i,q}^{*}$ and the first d_q observations are diseased biomarker results, denoted as $T_{i_1,q}^{d*}, i_1 = 1 \ldots d_q$, and the rest of the observations are nondiseased biomarker results, denoted as $T_{i_2,q}^{\bar{d}*}, i_2 = d_q + 1, \ldots, I$. The ROC curve and corresponding AUC could be estimated by the resampled data $(\mathbf{T}_{i_1,q}^{d*}, \mathbf{T}_{i_2,q}^{\bar{d}*})$ using the ROC methods, which could be either the parametric binormal method, the nonparametric empirical method, or the semiparametric method. We have

$T^{d*}_{i_1,q}$ follows distribution F and $T^{\bar{d}*}_{i_2,q}$ follows distribution G. The ROC curve is

$$\widehat{ROC}^*_q(u) = 1 - \hat{F}^*_q(\hat{G}^{*-1}_q(1-u)), \tag{2.1}$$

and the corresponding wAUC is

$$\widehat{wAUC}^*_q = \int_0^1 \widehat{ROC}^*_q(u)dW(u). \tag{2.2}$$

Hence the within cluster resampling (WCR) wAUC estimator is estimated by

$$\widehat{wAUC}_{WCR} = \frac{1}{Q}\sum_{q=1}^{Q} \widehat{wAUC}^*_q. \tag{2.3}$$

The within-cluster resampling (WCR) AUC estimator can be obtained by averaging all the $\widehat{AUC}^*_q$ and is estimated by

$$\widehat{AUC}_{WCR} = \frac{1}{Q}\sum_{q=1}^{Q} \widehat{AUC}^*_q. \tag{2.4}$$

The variance of WCR AUC is estimated by

$$\widehat{var}(\widehat{AUC}_{WCR}) = \frac{1}{Q}\sum_{q=1}^{Q} \widehat{var}(\widehat{AUC}^*_q) - S^2_{AUC}, \tag{2.5}$$

where

$$S^2_{AUC} = \frac{1}{Q-1}\sum_{q=1}^{Q}(\widehat{AUC}^*_q - \widehat{AUC}_{WCR})^2, \tag{2.6}$$

is the variability of the resampled AUC estimators. We note that, $\frac{1}{Q}\sum_{q=1}^{Q} \widehat{var}(\widehat{AUC}^*_q)$ can be

written in the sum of two parts, with one being the average of conditional expectation of variance and the other one being the average of conditional variance of expectation on all the resampled data sets.

$$\frac{1}{Q}\sum_{q=1}^{Q}\widehat{var}(\widehat{AUC}_q^*) = \widehat{var}\{E(\frac{1}{Q}\sum_{q=1}^{Q}\widehat{var}(\widehat{AUC}_q^*))|data\} + E\{var(\widehat{AUC}_q^*)|data\}, \qquad (2.7)$$

where $\widehat{var}\{E(\frac{1}{Q}\sum_{q=1}^{Q}\widehat{var}(\widehat{AUC}_q^*))|data\}$ is the WCR AUC variance is the conditional variance of the expectation of averaging all the resampled variance on all the resampled data sets and $E\{var(\widehat{AUC}_q^*)|data\}$ is the average of conditional expectation of variance of the Q estimators on all the resampled data sets $(\mathbf{T}_{i_1,q}^{d*}, \mathbf{T}_{i_2,q}^{\bar{d}*})$. We denote $E\{var(\widehat{AUC}_q^*)|data\}$ as S_{AUC}^2. So that, the WCR AUC variance equals to $\frac{1}{Q}\sum_{q=1}^{Q}\widehat{var}(\widehat{AUC}_q^*)$ subtract S_{AUC}^2.

Table 2.1 gives the major steps of within cluster resampling method on cluster ROC data

Table 2.1: Schematic representation of WCR ROC methods on evaluating one biomarker

	$\mathbf{T}^d, \mathbf{T}^{\bar{d}}$				
	$\downarrow$				
1	$\mathbf{T}_{i_1,1}^{d*}, \mathbf{T}_{i_2,1}^{\bar{d}*}$	$\rightarrow$	$\widehat{ROC}_1^*(u)$	$\rightarrow$	$\widehat{AUC}_1^*, \widehat{var}(\widehat{AUC}_1^*)$
2	$\mathbf{T}_{i_1,2}^{d*}, \mathbf{T}_{i_2,2}^{\bar{d}*}$	$\rightarrow$	$\widehat{ROC}_2^*(u)$	$\rightarrow$	$\widehat{AUC}_2^*, \widehat{var}(\widehat{AUC}_2^*)$
$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$
Q	$\mathbf{T}_{i_1,Q}^{d*}, \mathbf{T}_{i_2,Q}^{\bar{d}*}$	$\rightarrow$	$\widehat{ROC}_Q^*(u)$	$\rightarrow$	$\widehat{AUC}_Q^*, \widehat{var}(\widehat{AUC}_Q^*)$
					$\Downarrow$
					$\widehat{AUC}_{WCR}, \widehat{var}(\widehat{AUC}_{WCR}), S_{AUC}^2$

Note that, comparing to Obuchowski's and Li and Zhou's methods, the ROC curve estimated by the WCR methods is on a patient/subject level, which means, each resampled data set represents the biomarker results of the corresponding patients, not the locations. The WCR methods average all the possible resampled ROC curves. The TPR and FPR estimated by the WCR methods, are the probability of identifying a diseased patient when the patient is truly diseased and the probability of identifying a diseased patient when the patient is not diseased at different thresholds. For the qth

resampled data, the TPR and FPR can be written as $\widehat{TPR}_q(c) = P(T^{d*}_{i_1,q} > c)$ and $\widehat{FPR}_q(c) = P(T^{\bar{d}*}_{i_2,q} > c)$, where c is the thresholds. Let $\tilde{u}$ be the patient level false positive rate and $\widehat{ROC}_q(\tilde{u})$ be the patient level true positive rate, the qth ROC curve is given by $\widehat{ROC}_q(\tilde{u}) = 1 - \hat{F}_q(\hat{G}_q^{-1}(1 - \tilde{u}))$, where $\hat{F}_q(c) = 1 - \widehat{TPR}_q(c)$ and $\hat{G}_q(c) = 1 - \widehat{FPR}_q(c)$. The WCR ROC curve can be obtained by averaging all the ROC curves estimated using all the resampled data. The qth AUC estimator is $\widehat{AUC}^*_q = P(\tilde{T}^{d*}_{i_1,q} > \tilde{T}^{\bar{d}*}_{i_2,q})$. By averaging all the $\widehat{AUC}^*_q$, we can get the WCR AUC estimator. It can be expressed in probability as $\widehat{AUC}_{WCR} = P(\tilde{T}^d_i > \tilde{T}^{\bar{d}}_{i''})$, where i and i'' are not the same. $\tilde{T}^d_i$ and $\tilde{T}^{\bar{d}}_{i'}$ are the biomarker results of all the patients. Hence, $\widehat{AUC}_{WCR}$ is the probability that a diseased result from a randomly selected subject being greater than a nondiseased result from another randomly selected subject. Meanwhile, the AUC estimated by Obuchowski and Li and Zhou is $\widehat{AUC} = P(T^d_{ij} > T^{\bar{d}}_{i'k})$, which is the probability that a diseased result from a randomly selected location being greater than a nondiseased result from another randomly selected location. The difference of proposed method and Obuchowski's and Li and zhou's methods is that, the AUC of proposed method measures the accuracy of the biomarker on patients, but the AUC from other methods measure the accuracy of the biomarker on locations of the patients.

2.1.1 Parametric WCR Methods

The parametric binormal method can be employed to estimate the ROC curve and the AUC. For the qth resample, the diseased biomarker results $T^{d*}_{i_1,q}$ follows a normal distribution $N(\mu_D, \sigma^2_D)$ and nondiseased biomarker results $T^{\bar{d}*}_{i_2,q}$ follows a normal distribution $N(\mu_{\bar{D}}, \sigma^2_{\bar{D}})$. Under the normal assumption, there are two approaches to estimate $AUC_{WCR,BN}$. In the first approach, we first estimate the parameter a and b by using each resampled data set, so that $\hat{a}^*_q = (\hat{\mu}_{D,q} - \hat{\mu}_{\bar{D},q})/\hat{\sigma}_{D,q}$ and $\hat{b}^*_q = \hat{\sigma}_{\bar{D},q}/\hat{\sigma}_{D,q}$, where $\hat{\mu}_{D,q} = \sum_{i_1=1}^{d_q} T^{d*}_{i_1,q}/d_q$, $\hat{\mu}_{\bar{D},q} = \sum_{i_2=d_q+1}^{I} T^{\bar{d}*}_{i_2,q}/(I - d_q)$, $\hat{\sigma}^2_{D,q} = \sum_{i_1=1}^{d_q}(T^{d*}_{i_1,q} - \hat{\mu}_{D,q})/(d_q - 1)$, $\hat{\sigma}^2_{\bar{D},q} = \sum_{i_2=d_q}^{I}(T^{\bar{d}*}_{i_2,q} - \hat{\mu}_{\bar{D},q})/(I - d_q - 1)$ are the sample means and variances of resampled diseased and nondiseased biomarker results. The variance-covariance

estimate of $\hat{a}_q^*$ and $\hat{b}_q^*$, are estimated by the following equations, $\widehat{var}(\hat{a}_q^*) = (d_q(\hat{a}_q^{*2}+2)+2(I-d_q)\hat{b}_q^{*2})/(2d_q(I-d_q))$, $\widehat{var}(\hat{b}_q^*) = (I\hat{b}_q^{*2})/(2d_q(I-d_q))$ and $\widehat{cov}(\hat{a}_q^*, \hat{b}_q^*) = (\hat{a}_q^*\hat{b}_q^*)/(2(I-d_q))$. Then the WCR binormal model parameters can be estimated by averaging all the $\hat{a}_q^*$ and $\hat{b}_q^*$, which are given by $\hat{a}_{WCR} = \frac{1}{Q}\sum_{q=1}^{Q}\hat{a}_q^*$, $\hat{b}_{WCR} = \frac{1}{Q}\sum_{q=1}^{Q}\hat{b}_q^*$. The WCR ROC curve can be estimated by the WCR binormal model parameters and the WCR ROC estimator is

$$\widehat{ROC}_{WCR,BN_1} = \Phi(\hat{a}_{WCR} + \hat{b}_{WCR}\Phi^{-1}(u)). \tag{2.8}$$

The WCR AUC estimator can be estimated by taking the integral on the estimated WCR ROC curve, that is,

$$\widehat{AUC}_{WCR,BN_1} = \int_0^1 \widehat{ROC}_{WCR,BN_1}(u)du. \tag{2.9}$$

The explicit form of the WCR AUC estimator using WCR binormal model parameters $\hat{a}_{WCR}$ and $\hat{b}_{WCR}$ is,

$$\widehat{AUC}_{WCR,BN_1} = \Phi\left(\frac{\hat{a}_{WCR}}{\sqrt{1+\hat{b}_{WCR}^2}}\right). \tag{2.10}$$

Based on Equation 2.5, the WCR AUC variance is estimated by the following equations

$$\widehat{var}(\widehat{AUC}_{WCR,BN_1}) = \hat{f}_{WCR}^2\widehat{var}(\hat{a}_{WCR})+\hat{g}_{WCR}^2\widehat{var}(\hat{b}_{WCR})+2\hat{g}_{WCR}^2\hat{f}_{WCR}^2\widehat{cov}(\hat{a}_{WCR},\hat{b}_{WCR}), \tag{2.11}$$

where the parameters $\hat{f}_{WCR}$ and $\hat{g}_{WCR}$ are given by $\hat{f}_{WCR} = \frac{1}{Q}\sum_{q=1}^{Q}\hat{f}_q^*$, $\hat{g}_{WCR} = \frac{1}{Q}\sum_{q=1}^{Q}\hat{g}_q^*$ with $\hat{f}_q^* = e^{-\hat{a}_q^{*2}/2(1+\hat{b}_q^{*2})}/\sqrt{2\pi(1+\hat{b}_q^{*2})}$, $\hat{g}_q^* = (\hat{a}_q^*\hat{b}_q^*e^{-\hat{a}_q^{*2}/2(1+\hat{b}_q^{*2})})/\sqrt{2\pi(1+\hat{b}_q^{*2})^3}$ and the variance-covariance estimates of $\hat{a}_{WCR}, \hat{b}_{WCR}$ are estimated by

$$\widehat{var}(\hat{a}_{WCR}) = \frac{1}{Q}\sum_{q=1}^{Q}\widehat{var}(\hat{a}_q^*) - \frac{1}{Q-1}\sum_{q=1}^{Q}(\hat{a}_q^* - \hat{a}_{WCR})^2,$$

$$\widehat{var}(\hat{b}_{WCR}) = \frac{1}{Q}\sum_{q=1}^{Q}\widehat{var}(\hat{b}_q^*) - \frac{1}{Q-1}\sum_{q=1}^{Q}(\hat{b}_q^* - \hat{b}_{WCR})^2,$$

$$\widehat{cov}(\hat{b}_{WCR}, \hat{b}_{WCR}) = \frac{1}{Q}\sum_{q=1}^{Q}\widehat{cov}(\hat{b}_{WCR}, \hat{b}_q^*) - \frac{1}{Q-1}\sum_{q=1}^{Q}(\hat{a}_q^* - \hat{a}_{WCR})(\hat{b}_q^* - \hat{b}_{WCR}).$$

In the second approach, after the parameters $\hat{a}_q^*$ and $\hat{b}_q^*$ are estimated for the qth resampled data set, the qth ROC estimator is given by $\widehat{ROC}_q^* = \Phi(\hat{a}_q^* + \hat{b}_q^*\Phi^{-1}(u))$, the qth AUC estimator is $\widehat{AUC}_q^* = \int_0^1 \widehat{ROC}_q^*(u)du$, and explicit form of AUC_q using qth resampled parameters $\hat{a}_q^*$ and $\hat{b}_q^*$ is $\widehat{AUC}_q^* = \Phi\left(\frac{\hat{a}_q^*}{\sqrt{1+\hat{b}_q^{*2}}}\right)$. The variance of $\widehat{AUC}_q^*$ is given by $\widehat{var}(\widehat{AUC}_q^*) = \hat{f}_q^{*2}\widehat{var}(\hat{a}_q^*) + \hat{g}_q^{*2}\widehat{var}(\hat{b}_q^*) + 2\hat{f}_q^*\hat{g}_q^*\widehat{cov}(\hat{a}_q^*, \hat{b}_q^*)$. So that the WCR AUC estimator is the average of all the $\widehat{AUC}_q^*$,

$$\widehat{AUC}_{WCR,BN_2} = \frac{1}{Q}\sum_{q=1}^{Q}\widehat{AUC}_q^*, \tag{2.12}$$

and the WCR AUC variance estimator is given by

$$\widehat{var}(\widehat{AUC}_{WCR,BN_2}) = \frac{1}{Q}\sum_{q=1}^{Q}\widehat{var}(\widehat{AUC}_q^*) - S^2_{AUC,BN_2}, \tag{2.13}$$

where

$$S^2_{AUC,BN_2} = \frac{1}{Q-1}\sum_{q=1}^{Q}(\widehat{AUC}_q^* - \widehat{AUC}_{WCR,BN_2})^2, \tag{2.14}$$

is the variability of the resampled estimators.

2.1.2 Nonparametric WCR Methods

We can also apply the WCR methods on clustered ROC data by using the nonparametric method to estimate the ROC curve. For the qth resampled data, the empirical distributions of $X^*_{i_1,q}$ and $Y^*_{i_2,q}$ are $\hat{F}^*_{q,NP}(c) = \frac{1}{d_q}\sum_{i_1=1}^{d_q} I(T^{d*}_{i_1,q} \leq c)$ and $\hat{G}^*_{q,NP}(c) = \frac{1}{I-d_q}\sum_{i_2=d_q+1}^{I} I(T^{\bar{d}*}_{i_2,q} \leq c)$. Since the qth resampled data set is independent ROC data, the qth area under empirical ROC curve is estimated by the Wilcoxon U statistics,

$$\widehat{AUC}^*_{q,NP} = \frac{1}{d_q(I-d_q)}\sum_{i_1=1}^{d_q}\sum_{i_2=d_q+1}^{I}\Psi(T^{d*}_{i_1,q}, T^{\bar{d}*}_{i_2,q}), \tag{2.15}$$

where $\Psi(T^{d*}_{i_1,q}, T^{\bar{d}*}_{i_2,q}) = 1$ if $T^{d*}_{i_1,q} > T^{\bar{d}*}_{i_2,q}$ $\Psi(T^{d*}_{i_1,q}, T^{\bar{d}*}_{i_2,q}) = \frac{1}{2}$ if $T^{d*}_{i_1,q} = T^{\bar{d}*}_{i_2,q}$ $\Psi(T^{d*}_{i_1,q}, T^{\bar{d}*}_{i_2,q}) = 0$ if $T^{d*}_{i_1,q} < T^{\bar{d}*}_{i_2,q}$. and the variance of $\widehat{AUC}^*_{q,NP}$ is estimated by

$$\widehat{var}(\widehat{AUC}^*_{q,NP}) = \frac{V^*_{T^d,q}}{d_q} + \frac{V^*_{T^{\bar{d}},q}}{I-d_q}, \tag{2.16}$$

where $V^*_{T^d,q}$ and $V^*_{T^{\bar{d}},q}$ are the variance components generated by $T^{d*}_{i_1,q}$ and $T^{\bar{d}*}_{i_2,q}$, and they have the following forms,

$$V^*_{T^d,q} = \frac{1}{d_q-1}\sum_{i_1=1}^{d_q}[\frac{1}{I-d_q}\sum_{i_2=d_q+1}^{I}\Psi(T^{d*}_{i_1,q}, T^{\bar{d}*}_{i_2,q}) - \widehat{AUC}^*_{q,NP}]^2,$$

and

$$V^*_{T^{\bar{d}},q} = \frac{1}{I-d_q-1}\sum_{i_2=d_q+1}^{I}[\frac{1}{d_q}\sum_{i_1=1}^{d_q}\Psi(T^{d*}_{i_1,q}, T^{\bar{d}*}_{i_2,q}) - \widehat{AUC}^*_{q,NP}]^2.$$

The empirical WCR AUC estimator is the average of $\widehat{AUC}^*_{q,NP}$

$$\widehat{AUC}_{WCR,NP} = \frac{1}{Q}\sum_{q=1}^{Q}\widehat{AUC}^*_{q,NP}, \tag{2.17}$$

and the WCR AUC variance can be estimated by the following equations,

$$\widehat{var}(\widehat{AUC}_{WCR,NP}) = \frac{1}{Q}\sum_{q=1}^{Q}\widehat{var}(\widehat{AUC}^*_{q,NP}) - S^2_{AUC,NP}, \tag{2.18}$$

where

$$S^2_{AUC,NP} = \frac{1}{Q-1}\sum_{q=1}^{Q}(\widehat{AUC}^*_{q,NP} - \widehat{AUC}_{WCR,NP})^2, \tag{2.19}$$

is the variability of the resampled estimators.

The nonparametric WCR methods are similar to the second approach of parametric WCR methods. They both estimate the resampled estimators $\widehat{AUC}^*_q$ and $\widehat{var}(\widehat{AUC}^*_q)$ first. And then take the average of all the resampled estimators. Note that for WCR AUC variance, the variability of the resampled estimators should be subtracted because all the resampled data are correlated. Meanwhile, the first approach of parametric WCR method estimated the WCR parameter estimators $\hat{a}_{WCR}$ and $\hat{b}_{WCR}$ first, and use the WCR parameter estimators to evaluate the WCR ROC curve, WCR AUC and WCR AUC variance. In the second approach, we first average the Q empirical distributions $\hat{F}^*_{q,NP}(c)$ and $\hat{G}^*_{q,NP}(c)$, where $q = 1, \ldots, Q$. We then have the following estimators

$$\hat{F}_{WCR,NP_2} = \frac{1}{Q}\sum_{q=1}^{Q}\hat{F}^*_{q,NP}(c), \tag{2.20}$$

$$\hat{G}_{WCR,NP_2} = \frac{1}{Q}\sum_{q=1}^{Q}\hat{G}^*_{q,NP}(c), \tag{2.21}$$

for F and G respectively. Then the empirical WCR ROC curve is estimated by

$$\widehat{ROC}_{WCR,NP_2}(u) = 1 - \hat{F}_{WCR,NP_2}(\hat{G}^{-1}_{WCR,NP_2}(1-u)), \tag{2.22}$$

and the WCR wAUC is estimated by

$$\widehat{wAUC}_{WCR,NP_2} = \int_0^1 \widehat{ROC}_{WCR,NP_2}(u)dW(u). \tag{2.23}$$

The kernel estimator can be used to fit the resampled dataset to yield a smooth ROC estimator. The distributions of the qth resampled dataset $T^{d*}_{i_1,q}$ and $T^{\bar{d}*}_{i_2,q}$ are estimated by

$$\hat{F}^*_{q,KN}(c) = \frac{1}{d_q h}\sum_{i_1=1}^{d_q} K\left(\frac{c - T^{d*}_{i_1,q}}{h}\right), \tag{2.24}$$

$$\hat{G}^*_{q,KN}(c) = \frac{1}{(I-d_q)h}\sum_{i_2=d_q+1}^{I} K\left(\frac{c - T^{\bar{d}*}_{i_2,q}}{h}\right), \tag{2.25}$$

where h is the kernel bandwidth and the function $K()$ is the kernel. In order to $\widehat{AUC}_{WCR}$, we can use two approaches here. In the first approach, we fit the qth ROC curve $ROC^*_{q,KN}$ using the qth estimated kernel distributions $\hat{F}^*_{q,KN}(c)$ and $\hat{G}^*_{q,NP}(c)$. The corresponding weighted area under the qth ROC curve $AUC^*_{q,KN}$ is estimated by

$$\widehat{wAUC}_{WCR,KN} = \int_0^1 \widehat{ROC}_{WCR,KN}(u)dW(u). \tag{2.26}$$

Then we average the Q $wAUC^*_{q,KN}$ by

$$\widehat{wAUC}_{WCR,KN_1} = \frac{1}{Q}\sum_{q=1}^{Q} \widehat{wAUC}^*_{q,KN}. \tag{2.27}$$

In the other approach, the average of Q distributions $\hat{F}^*_{q,NP}(c)$ and $\hat{G}^*_{q,NP}(c)$, where $q = 1, \ldots, Q$, are obtained. Then, we fit the WCR ROC curve by

$$\widehat{ROC}_{WCR,KN_2}(u) = 1 - \hat{F}_{WCR,KN}(\hat{G}^{-1}_{WCR,KN}(1-u)), \tag{2.28}$$

and the WCR wAUC is estimated by

$$\widehat{wAUC}_{WCR,KN_2} = \int_0^1 \widehat{ROC}_{WCR,KN_2}(u)dW(u). \tag{2.29}$$

2.1.3 Semiparametric WCR Methods

For the semiparametric WCR methods, we could employ the generalized linear model. For the generalized linear model in Equation (1.44), we have one biomarker and the model became

$$ROC(u) = g\{\boldsymbol{\beta} h(u)\} = g\{\beta_1 + \beta_2 h^{-1}(u)\}, \tag{2.30}$$

For the qth resample, we use the generalized linear model method estimating equation to estimate the parameters $\hat{\boldsymbol{\beta}}^*_{q,GLM}$. Let the indicator variable $U^*_{q,i_1i_2} = I[T^{d*}_{q,i_1} \geq T^{\bar{d}*}_{q,i_2}]$, we solve $\hat{\boldsymbol{\beta}}^*_{q,GLM}$ by solving

$$\sum_{i_1=1}^{d_q}\sum_{i_2=d_q+1}^{Q} \frac{U^*_{q,i_1i_2} - g\{\beta^*_{q,GLM}h(u_q)\}}{g\{\beta^*_{q,GLM}h(u_q)\}(1-g\{\beta^*_{q,GLM}h(u_q)\})}\frac{\partial g\{\beta^*_{q,GLM}h(u_q)\}}{\partial \beta^*_{q,GLM}} = 0 \tag{2.31}$$

The ROC curve is estimated from the qth resample by

$$\widehat{ROC}^{*}_{q,GLM}(u_q) = g\{\hat{\boldsymbol{\beta}}^{*}_{q,GLM} h(u_q)\},$$

and the wAUC is

$$\widehat{wAUC}^{*}_{q,GLM} = \int_0^1 \widehat{ROC}^{*}_{q,GLM}(u) dW(u).$$

So the $\widehat{AUC}^{*}_{q,GLM}$ are averaged to obtain an estimator for the AUC.

The other way to estimate the parameters is the least square method. The least square estimator is

$$\hat{\boldsymbol{\beta}}^{*}_{q,LS} = (M_q^T M_q)^{-1} M_q^T \tilde{\boldsymbol{T}}_q^{\bar{d}*},$$

where M_q is the design matrix and $\tilde{\boldsymbol{T}}_q^{\bar{d}*} = g^{-1}(ROC^{*}_{q}(u_q))$. So that we could estimate the qth ROC curve and corresponding wAUC. The WCR wAUC estimator is the average of Q $\widehat{wAUC}^{*}_{q,LS}$

2.2 Simulation Study

2.2.1 Simulation Study for the AUC Estimator

In this section, we report simulation studies to evaluate the performance of the proposed WCR methods. In particular, we are interested in whether the proposed methods can account for the within-cluster correlation and provide valid AUC and variance estimators. We focus primarily on the coverage percentage of the confidence intervals estimated by the proposed methods. We perform our methods on simulated clustered ROC data and estimate the WCR AUC and the WCR AUC variance by the parametric WCR methods and the nonparametric WCR method. We compare our methods with the traditional methods and show the bias in using the traditional methods on clustered ROC data. The WCR methods are also compared with Obuchowski's method. The simulation results from these two methods are on different levels. The WCR methods are on patient level and the Obuchowski's method is on location level. We consider the situation where, for a diseased subject,

there are either 2 or 5 diseased results plus 1 nondiseased result, for a nondiseased subject, all biomarker results in the same cluster are nondiseased.

Let I_1 and I_0 denote the number of clusters in the diseased group and the nondiseased group. We let the two groups have the same number of clusters, so that $I_1 = I_0 = I/2$. The clusters in the diseased group have a cluster size $m_i = 3$ with probability p and a cluster size $m_i = 6$ with probability $1 - p$, where as the clusters in the nondiseased group have a cluster size $n_j = 2$ with probability $1 - p$ and a cluster size $n_j = 5$ with probability p. We simulate 1000 clustered ROC data from normal and lognormal distributions, respectively:

1. $T^d \sim N(\mu_{T^d}, \mathbf{\Sigma}_{T^d})$ and $T^{\bar{d}} \sim N(\mu_{T^{\bar{d}}}, \mathbf{\Sigma}_{T^{\bar{d}}})$, where $\boldsymbol{\mu}_{T^d} = (1, 1, 0)$ when $m_i = 3$ and $\boldsymbol{\mu}_{T^d} = (1, 1, 1, 1, 1, 0)$ when $m_i = 6$, $\boldsymbol{\mu}_{T^{\bar{d}}} = (0, 0)$ when $n_j = 2$ and $\boldsymbol{\mu}_{T^{\bar{d}}} = (0, 0, 0, 0, 0)$ when $n_j = 5$. The variance-covariance matrix $\mathbf{\Sigma}_{T^d}$ is a $m_i \times m_i$ matrix with diagonal elements equal to 1 and correlation coefficients equal to ρ and $\mathbf{\Sigma}_{T^{\bar{d}}}$ is a $n_j \times n_j$ matrix with diagonal elements equal to 1 and correlation coefficients equal to ρ

2. $T^d \sim LogNormal(\mu_{T^d}, \mathbf{\Sigma}_{T^d})$ and $T^{\bar{d}} \sim LogNormal(\mu_{T^{\bar{d}}}, \mathbf{\Sigma}_{T^{\bar{d}}})$, with the same settings on μ_{T^d}, $\mathbf{\Sigma}_{T^d}$, $\mu_{T^{\bar{d}}}$, $\mathbf{\Sigma}_{T^{\bar{d}}}$, m_i, n_j and ρ.

We let p, the informative cluster size correlation, be 0.3, 0.4 and 0.5. Note that when $p \neq 0.5$, the cluster size is different between the two groups. Under each setting, we let ρ, the within-cluster correlation, be 0.2, 0.5, 0.9 and $I/2$, the number of clusters in each group, be 25, 50 and 100.

For the simulated normal clustered ROC data, we employ the proposed parametric WCR methods and nonparametric WCR method, as well as traditional parametric and nonparametric methods and Obuchowski's method. For the simulated lognormal clustered ROC data, we apply the nonparametric WCR method, traditional nonparametric method and Obuchowski's method. Li and Zhou's method gives the same estimator as Obuchowski's method, and is not compared in the simulation study. We obtain the AUC estimators and 95% confidence intervals from all the methods. Biases, square root of mean squared errors, and simulated coverage percentage of 95% confidence intervals under various scenarios are shown in the tables.

In Table 2.2, we compare the proposed parametric WCR methods with the traditional parametric

method when the data are normal. In Tables 2.3 and 2.4, we compare the proposed nonparametric WCR methods, traditional nonparametric method (DeLong, DeLong, and Clarke-Pearson 1988), and the Obuchowski's nonparametric method (Obuchowski 1997) using simulated normal and log-normal data. It is clear that the coverage percentages obtained by our methods are close to the nominal level and do not change as the within-cluster correlation becomes larger. Also the biases obtained by the proposed methods are close to zero. This indicates that proposed WCR methods have a good performance on clustered ROC data and can account for the within-cluster correlation. On the contrary, the coverage percentages obtained by the traditional methods are not close to 95% and as within-cluster correlation increases, the coverage percentages decrease. Our methods handle the within-cluster correlation better than the traditional methods do. The simulation results for the average length of 95% confidence intervals show that the WCR and the Obuchowski's methods give similar confidence interval length but the traditional method estimate a smaller length. As ρ increases, the length increases. As sample size increases, the length decreases. In Table 2.4, we compare the nonparametric WCR methods with the traditional nonparametric method when the normal assumption is violated. The WCR methods work well on lognormal data and obtain better coverage percentages than those from the traditional nonparametric method. The results obtained by the WCR methods and the Obuchowski's method are similar, which indicate that the biomarker has similar accuracy on patients and locations.

In Figures 2.1, 2.2, 2.3, 2.4, 2.5, and 2.6. we visualize the simulation results for the coverage percentage of the 95% confidence intervals and the average length of the 95% confidence intervals.

2.2.2 Simulation Study for the ROC Curve

In this section, we report simulation studies for the empirical WCR ROC curves and traditional empirical ROC curves. In particular, we are interested in whether the proposed methods can fit a smoother ROC curve for clustered ordinal ROC data. We focus primarily on the visualization of the simulation and the standard deviation of the adjoint point difference of the empirical WCR ROC curves and traditional empirical ROC curves. We perform our methods on simulated normal and lognormal clustered ordinal ROC data and fit the empirical WCR ROC curves for each simulation.

Table 2.2: Simulation results for normal clustered ROC data using three parametric methods

			WCR1				WCR2				Parametric			
p	ρ	n	Bias (%)	RMSE	CP	Length	Bias (%)	RMSE	CP	Length	Bias (%)	RMSE	CP	Length
0.3	0.2	25	0.2314	0.0499	0.930	0.1609	-0.1819	0.0436	0.928	0.1644	-0.1655	0.0494	0.866	0.1514
		50	0.1751	0.0333	0.955	0.1181	-0.0241	0.0292	0.952	0.1190	-0.1831	0.0336	0.873	0.1071
		100	0.1809	0.0253	0.945	0.0840	0.0846	0.0218	0.946	0.0843	-0.1339	0.0250	0.872	0.0758
	0.5	25	0.6092	0.0583	0.932	0.1894	0.2584	0.0507	0.926	0.1917	-0.0396	0.0614	0.796	0.1505
		50	0.1842	0.0417	0.949	0.1366	0.0185	0.0364	0.931	0.1372	-0.1217	0.0434	0.789	0.1066
		100	-0.0780	0.0295	0.943	0.0977	-0.1586	0.0251	0.950	0.0979	0.0656	0.0299	0.788	0.0757
	0.9	25	0.4248	0.0677	0.935	0.2237	0.1942	0.0578	0.929	0.2261	0.4044	0.0742	0.688	0.1498
		50	0.0186	0.0491	0.953	0.1599	-0.0920	0.0412	0.943	0.1607	-0.1787	0.0528	0.681	0.1067
		100	-0.0154	0.0336	0.957	0.1142	-0.0697	0.0297	0.938	0.1144	0.2235	0.0363	0.702	0.0755
0.4	0.2	25	0.2494	0.0486	0.955	0.1598	-0.1618	0.0444	0.927	0.1636	0.0835	0.0474	0.875	0.1487
		50	0.1085	0.0346	0.943	0.1178	-0.0904	0.0311	0.930	0.1188	-0.0352	0.0342	0.861	0.1054
		100	-0.0527	0.0234	0.935	0.0842	-0.1493	0.0210	0.951	0.0845	-0.1123	0.0231	0.902	0.0746
	0.5	25	0.1288	0.0599	0.940	0.1881	-0.2210	0.0509	0.935	0.1907	-0.2606	0.0645	0.741	0.1485
		50	0.1849	0.0408	0.950	0.1360	0.0141	0.0353	0.938	0.1367	0.1816	0.0432	0.759	0.1054
		100	0.1579	0.0297	0.951	0.0971	0.0757	0.0257	0.946	0.0973	-0.0836	0.0310	0.776	0.0746
	0.9	25	0.2459	0.0691	0.947	0.2212	0.0006	0.0597	0.929	0.2237	0.2469	0.0762	0.651	0.1474
		50	0.0151	0.0477	0.955	0.1587	-0.1020	0.0424	0.933	0.1595	-0.1064	0.0518	0.662	0.1049
		100	0.0417	0.0339	0.944	0.1130	-0.0151	0.0276	0.958	0.1133	0.0215	0.0369	0.686	0.0745
0.5	0.2	25	0.2137	0.0489	0.933	0.1588	-0.2019	0.0433	0.928	0.1631	0.1707	0.0477	0.881	0.1476
		50	0.2414	0.0355	0.938	0.1168	0.0406	0.0301	0.937	0.1180	-0.0498	0.0344	0.869	0.1045
		100	0.1091	0.0244	0.951	0.0841	0.0100	0.0215	0.939	0.0844	-0.0641	0.0244	0.891	0.0739
	0.5	25	0.3181	0.0584	0.947	0.1860	-0.0416	0.0487	0.941	0.1891	-0.1598	0.0604	0.777	0.1474
		50	-0.1308	0.0407	0.952	0.1345	-0.2997	0.0358	0.935	0.1354	-0.2823	0.0424	0.787	0.1041
		100	-0.0882	0.0294	0.950	0.0963	-0.1726	0.0245	0.947	0.0966	-0.0445	0.0311	0.778	0.0739
	0.9	25	0.0674	0.0704	0.942	0.2167	-0.1827	0.0562	0.941	0.2198	0.0325	0.0763	0.670	0.1456
		50	-0.0079	0.0487	0.938	0.1566	-0.1303	0.0413	0.940	0.1575	0.1576	0.0526	0.672	0.1039
		100	0.0203	0.0342	0.938	0.1117	-0.0398	0.0290	0.944	0.1120	-0.1594	0.0369	0.687	0.0738

WCR1-the first parametric WCR method proposed in Section 2.1.1;
WCR2-the second parametric WCR method proposed Section 2.1.2;
Parametric-the parametric ROC method for independent data;
RMSE-square root of mean squared error;
Coverage-the coverage percentage of 95% confidence intervals;
Length- the average length of the 95% confidence intervals.

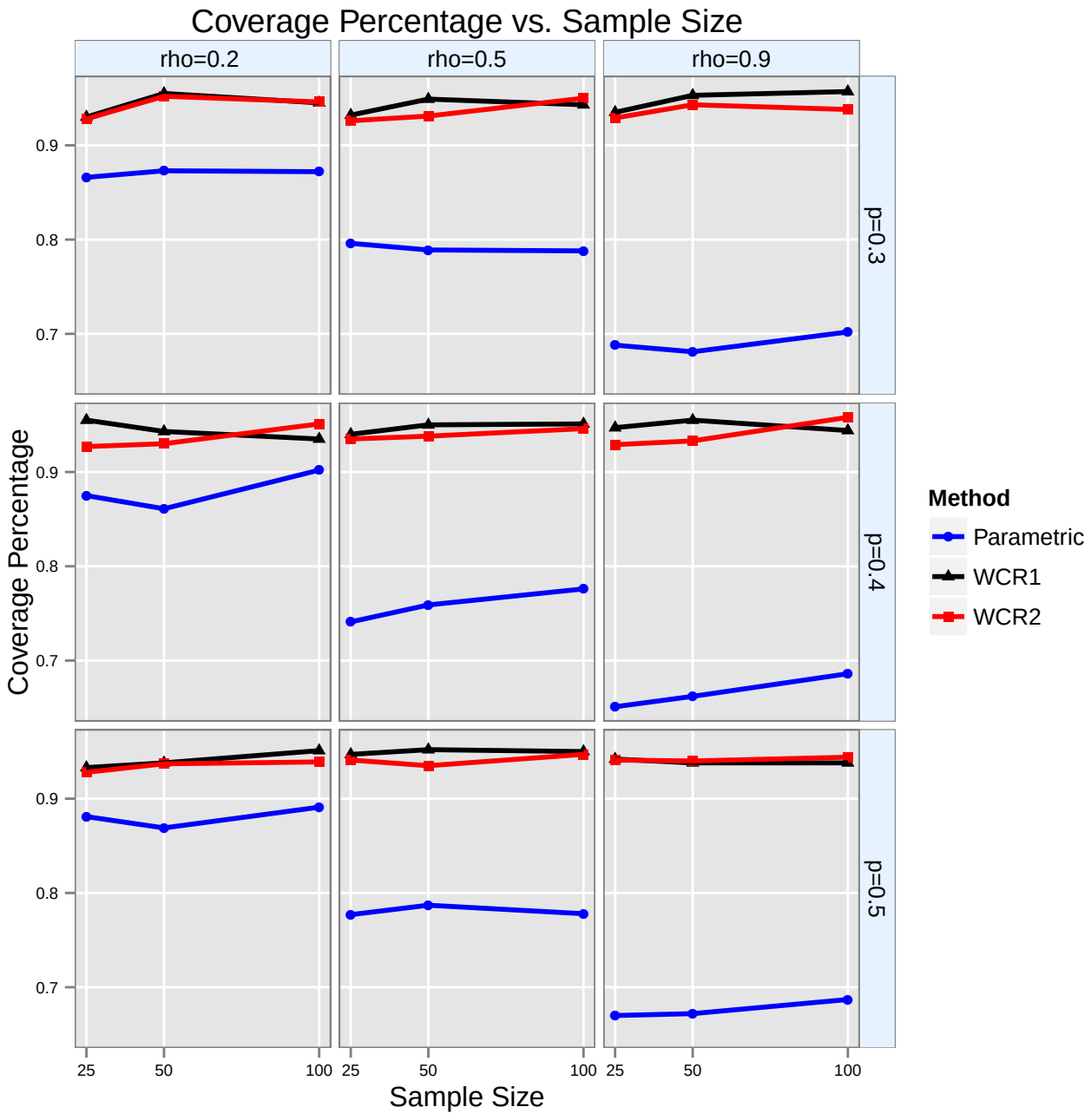

Figure 2.1: The coverage percentage of the 95% confidence intervals of the traditional parametric method and the two proposed parametric WCR methods for normal clustered ROC data

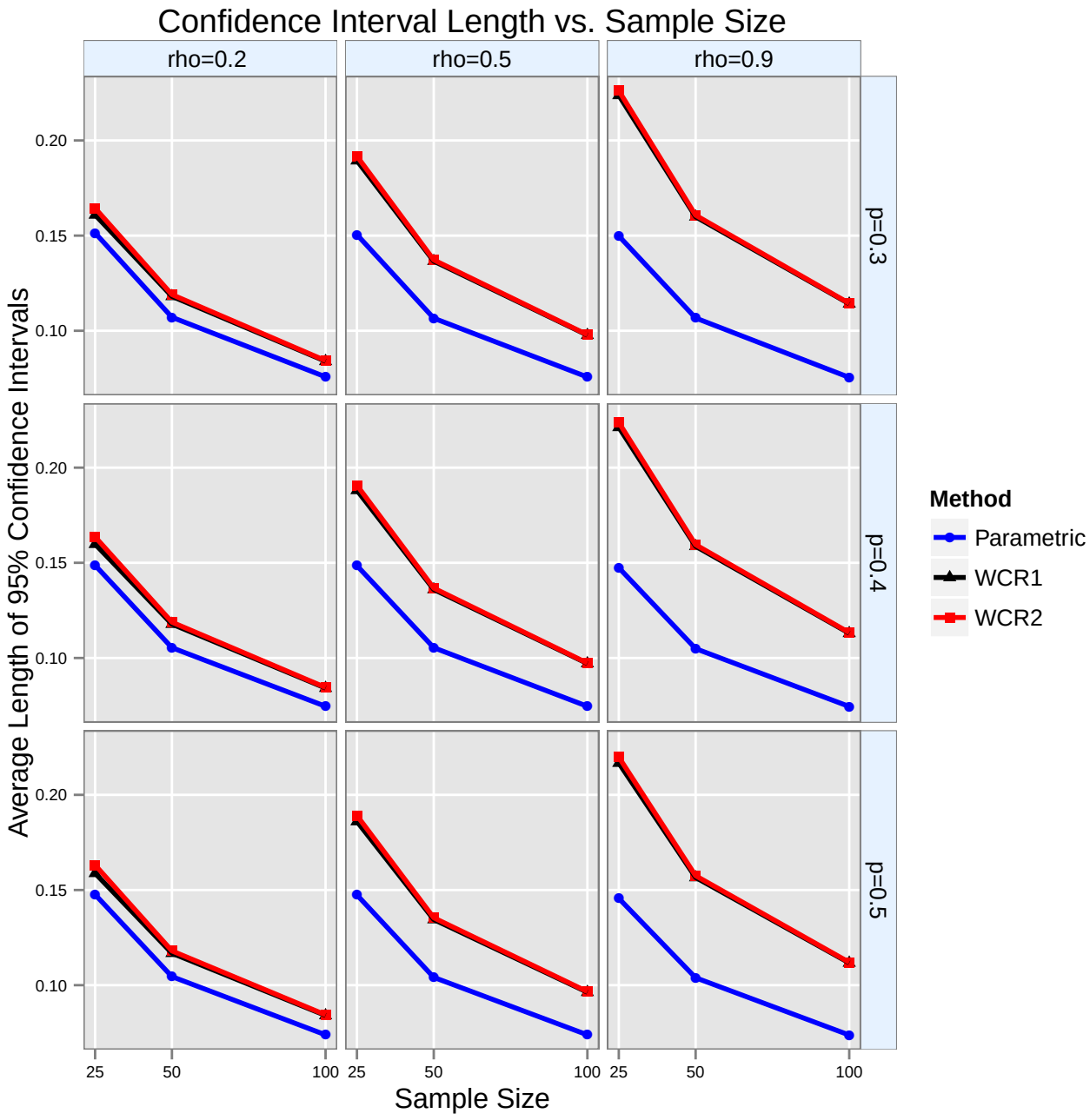

Figure 2.2: The average length of the 95% confidence intervals of the traditional parametric method and the two proposed parametric WCR methods for normal clustered ROC data

Table 2.3: Simulation results for normal clustered ROC data using three nonparametric methods

			WCR1				Obuchowski				Nonparametric			
p	ρ	n	Bias (%)	RMSE	CP	Length	Bias (%)	RMSE	CP	Length	Bias (%)	RMSE	CP	Length
0.3	0.2	25	0.1566	0.0499	0.930	0.1788	0.0833	0.0418	0.932	0.1642	-0.0961	0.0484	0.899	0.1441
		50	0.1954	0.0333	0.955	0.1244	0.1712	0.0291	0.951	0.1160	0.0788	0.0356	0.876	0.1016
		100	-0.0034	0.0253	0.945	0.0870	0.0171	0.0207	0.954	0.0821	-0.0694	0.0249	0.874	0.0717
	0.5	25	-0.0060	0.0583	0.932	0.2058	0.1459	0.0498	0.925	0.1935	-0.0424	0.0609	0.800	0.1442
		50	-0.0917	0.0417	0.949	0.1428	-0.0939	0.0349	0.947	0.1370	-0.1225	0.0425	0.802	0.1016
		100	-0.0471	0.0295	0.943	0.1002	-0.0504	0.0250	0.942	0.0968	-0.0562	0.0310	0.792	0.0717
	0.9	25	0.2794	0.0677	0.935	0.2405	0.6393	0.0595	0.924	0.2323	-0.2002	0.0724	0.711	0.1442
		50	-0.3751	0.0491	0.953	0.1676	-0.1642	0.0417	0.942	0.1639	0.0695	0.0498	0.719	0.1017
		100	0.0555	0.0336	0.957	0.1175	0.1503	0.0289	0.950	0.1158	-0.0015	0.0388	0.686	0.0716
0.4	0.2	25	0.2331	0.0486	0.955	0.1790	0.1652	0.0403	0.947	0.1669	-0.0022	0.0487	0.874	0.1444
		50	0.2728	0.0346	0.943	0.1248	0.2575	0.0308	0.948	0.1179	-0.0671	0.0349	0.881	0.1018
		100	0.0318	0.0234	0.935	0.0868	0.0172	0.0221	0.932	0.0833	-0.0508	0.0235	0.888	0.0719
	0.5	25	-0.2004	0.0599	0.940	0.2037	-0.0781	0.0523	0.926	0.1965	0.0497	0.0602	0.794	0.1440
		50	0.0916	0.0408	0.950	0.1424	0.1968	0.0357	0.938	0.1405	-0.0031	0.0420	0.798	0.1018
		100	0.0851	0.0297	0.951	0.1000	0.0717	0.0253	0.947	0.0992	0.0452	0.0317	0.777	0.0718
	0.9	25	0.1880	0.0691	0.947	0.2377	0.4304	0.0597	0.934	0.2386	0.3803	0.0773	0.692	0.1441
		50	0.0511	0.0477	0.955	0.1654	0.2071	0.0425	0.943	0.1681	-0.2059	0.0536	0.697	0.1013
		100	0.0180	0.0339	0.944	0.1162	0.1191	0.0305	0.951	0.1189	0.0966	0.0372	0.687	0.0717
0.5	0.2	25	0.0931	0.0489	0.933	0.1783	0.1562	0.0432	0.933	0.1683	0.0268	0.0485	0.878	0.1452
		50	0.1172	0.0355	0.938	0.1238	0.1032	0.0299	0.952	0.1186	0.1153	0.0350	0.884	0.1024
		100	-0.1124	0.0244	0.951	0.0873	-0.0899	0.0204	0.963	0.0845	0.0338	0.0243	0.885	0.0723
	0.5	25	-0.0994	0.0584	0.947	0.2028	-0.0291	0.0507	0.947	0.2010	-0.0839	0.0617	0.785	0.1449
		50	0.0330	0.0407	0.952	0.1411	0.0732	0.0364	0.942	0.1426	-0.1848	0.0427	0.805	0.1026
		100	-0.0651	0.0294	0.950	0.0990	0.0064	0.0251	0.954	0.1008	0.0316	0.0296	0.814	0.0723
	0.9	25	0.0149	0.0704	0.942	0.2364	0.0791	0.0621	0.932	0.2446	0.2142	0.0774	0.672	0.1452
		50	0.3122	0.0487	0.938	0.1641	0.4309	0.0453	0.925	0.1717	0.1994	0.0553	0.672	0.1021
		100	0.0075	0.0342	0.938	0.1151	0.0638	0.0317	0.936	0.1214	0.0789	0.0390	0.667	0.0721

WCR-the proposed nonparametric WCR method;
Obuchowski-Obuchowski's nonparametric method for clustered ROC data;
Nonparametric-the nonparametric ROC method for independent ROC data;
RMSE-square root of mean squared error;
CP-coverage percentage of 95% confidence intervals;
Length- the average length of the 95% confidence intervals.

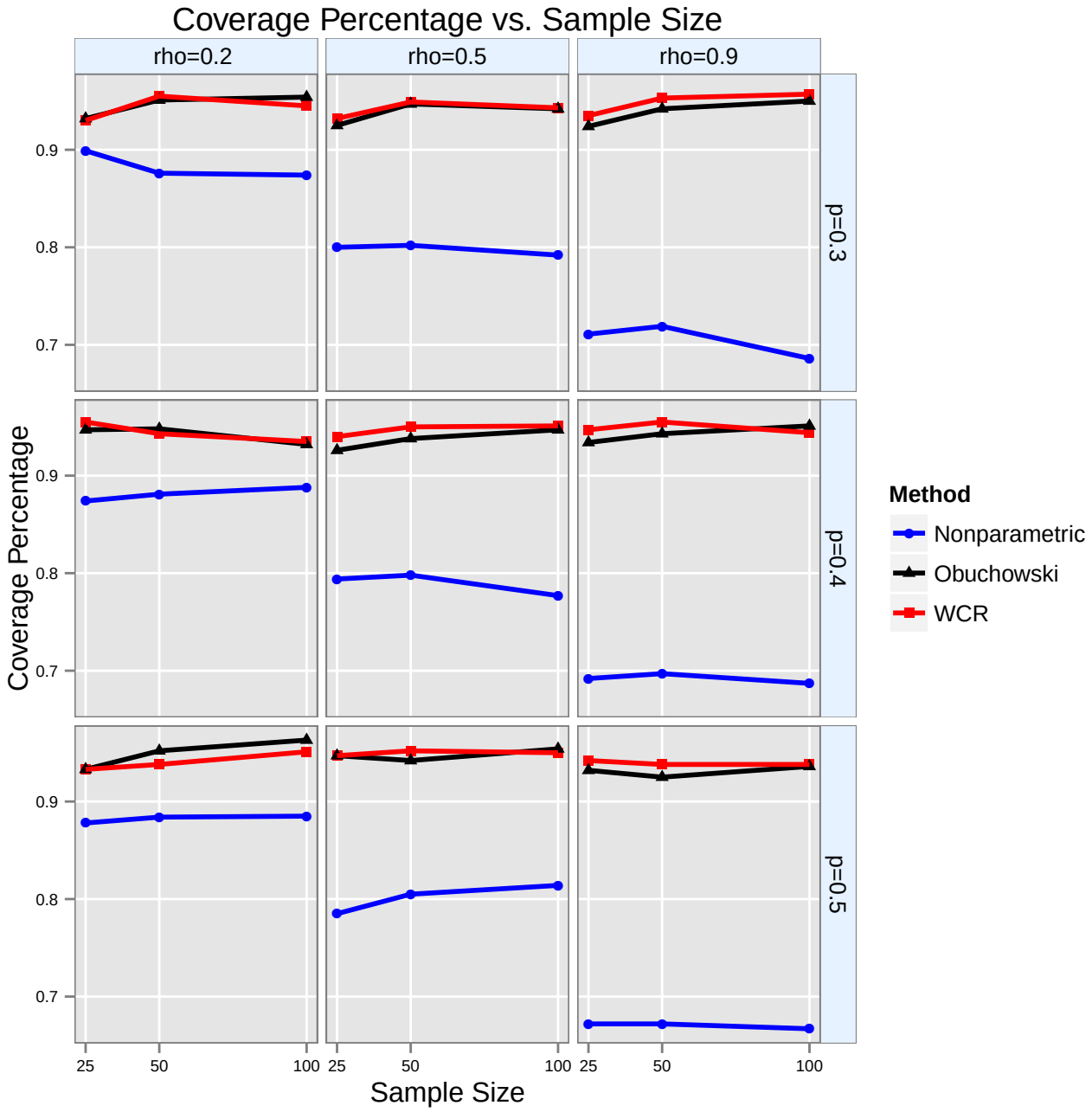

Figure 2.3: The coverage percentage of the 95% confidence intervals of the nonparametric method, Obuchowski's nonparametric method and proposed nonparametric WCR method for normal clustered ROC data

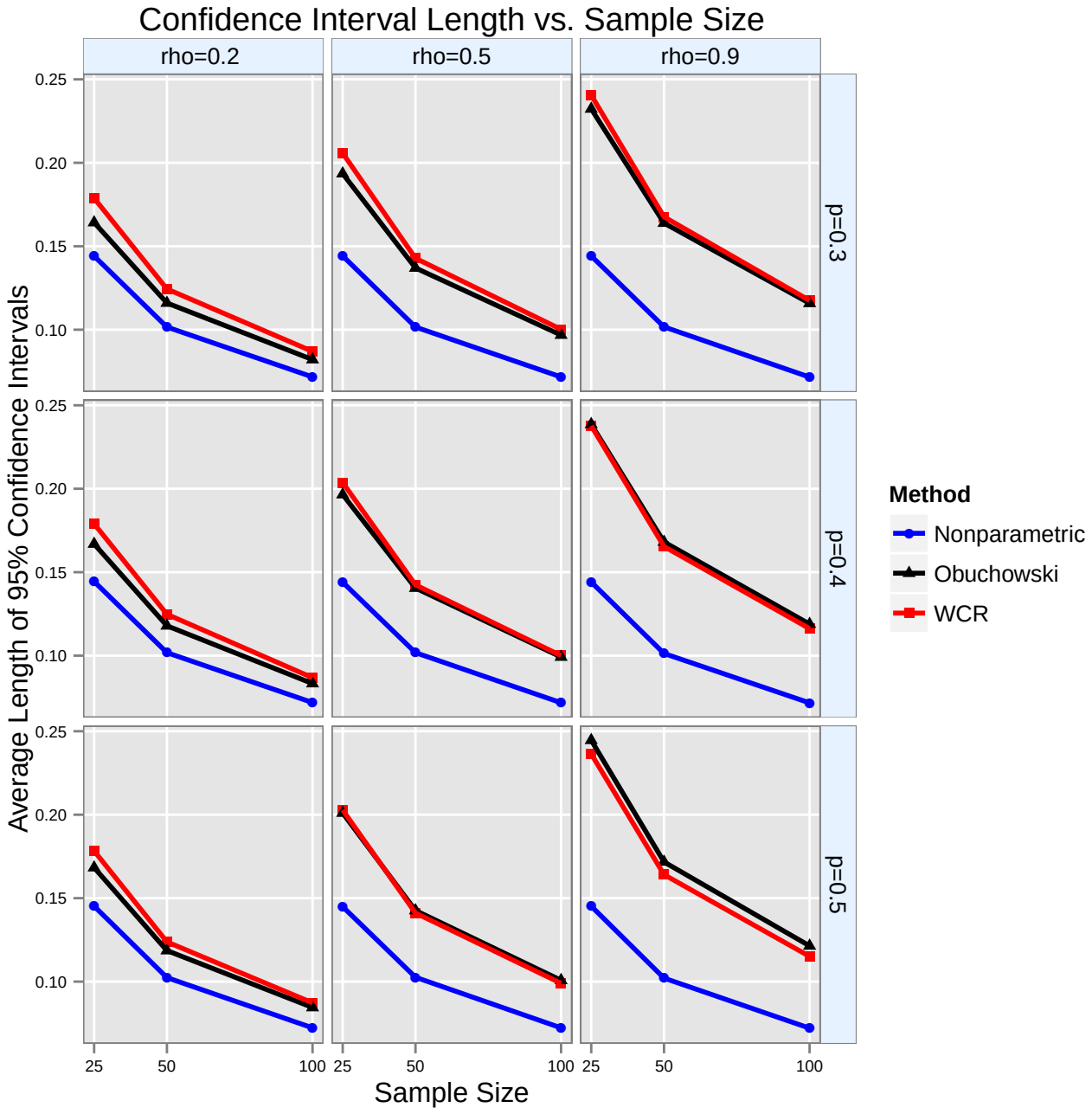

Figure 2.4: The average length of the 95% confidence intervals of the traditional nonparametric method, Obuchowski's nonparametric method and proposed nonparametric WCR methods for normal clustered ROC data

Table 2.4: Simulation results for lognormal clustered ROC data using three nonparametric methods

			WCR1				Obuchowski				Nonparametric			
p	ρ	n	Bias (%)	RMSE	CP	Length	Bias (%)	RMSE	CP	Length	Bias (%)	RMSE	CP	Length
0.3	0.2	25	-0.0018	0.0451	0.935	0.1797	-0.0051	0.0432	0.928	0.1643	0.1292	0.0495	0.879	0.1443
		50	-0.0773	0.0318	0.948	0.1249	-0.1095	0.0303	0.943	0.1161	0.0394	0.0344	0.878	0.1016
		100	-0.0506	0.0221	0.949	0.0873	-0.0522	0.0215	0.943	0.0821	0.0824	0.0242	0.893	0.0718
	0.5	25	0.3747	0.0522	0.933	0.2056	0.3418	0.0506	0.933	0.1931	0.1829	0.0620	0.779	0.1437
		50	-0.1874	0.0365	0.946	0.1433	-0.1052	0.0352	0.944	0.1370	-0.0218	0.0426	0.801	0.1017
		100	-0.0623	0.0257	0.945	0.1005	-0.0390	0.0249	0.951	0.0968	-0.1638	0.0307	0.784	0.0718
	0.9	25	-0.1356	0.0596	0.944	0.2406	0.1290	0.0587	0.936	0.2318	0.0777	0.0746	0.700	0.1438
		50	0.1068	0.0431	0.942	0.1678	0.2727	0.0423	0.930	0.1641	0.1251	0.0545	0.676	0.1014
		100	-0.0730	0.0301	0.940	0.1174	0.0214	0.0298	0.939	0.1160	-0.1281	0.0388	0.696	0.0717
0.4	0.2	25	0.3092	0.0451	0.941	0.1790	0.3334	0.0429	0.933	0.1662	-0.2417	0.0477	0.897	0.1443
		50	0.0184	0.0303	0.952	0.1241	0.0322	0.0291	0.937	0.1176	-0.0871	0.0348	0.889	0.1018
		100	0.0970	0.0213	0.957	0.0872	0.1051	0.0207	0.947	0.0832	-0.0339	0.0246	0.873	0.0719
	0.5	25	0.1131	0.0504	0.945	0.2040	0.2309	0.0503	0.936	0.1973	0.3286	0.0605	0.783	0.1441
		50	-0.0163	0.0352	0.953	0.1422	0.1101	0.0357	0.943	0.1401	0.0457	0.0440	0.786	0.1017
		100	-0.0564	0.0270	0.929	0.0996	-0.0062	0.0263	0.940	0.0989	0.1139	0.0314	0.777	0.0718
	0.9	25	0.2177	0.0587	0.937	0.2385	0.3996	0.0597	0.921	0.2385	-0.0269	0.0758	0.679	0.1439
		50	-0.1680	0.0422	0.948	0.1665	-0.0590	0.0438	0.947	0.1693	0.4538	0.0522	0.700	0.1017
		100	0.0611	0.0283	0.958	0.1165	0.1165	0.0290	0.954	0.1194	-0.0110	0.0382	0.684	0.0719
0.5	0.2	25	-0.0079	0.0452	0.936	0.1794	-0.0267	0.0441	0.943	0.1696	-0.0168	0.0504	0.873	0.1457
		50	-0.0249	0.0302	0.952	0.1244	0.0092	0.0301	0.945	0.1194	0.1180	0.0332	0.897	0.1024
		100	0.0619	0.0220	0.942	0.0867	0.0546	0.0213	0.952	0.0841	0.0096	0.0244	0.882	0.0723
	0.5	25	0.0863	0.0509	0.942	0.2042	0.1184	0.0522	0.931	0.2027	-0.0806	0.0600	0.796	0.1459
		50	0.0459	0.0358	0.947	0.1419	0.0882	0.0361	0.947	0.1425	0.0288	0.0423	0.795	0.1022
		100	-0.1065	0.0252	0.946	0.0991	-0.1444	0.0258	0.945	0.1008	-0.0785	0.0304	0.795	0.0723
	0.9	25	-0.1002	0.0584	0.935	0.2349	0.1372	0.0627	0.920	0.2429	0.1327	0.1022	0.500	0.1446
		50	0.0394	0.0410	0.949	0.1639	0.1798	0.0436	0.936	0.1718	0.1184	0.0525	0.703	0.1020
		100	-0.0084	0.0294	0.951	0.1151	0.0638	0.0312	0.951	0.1217	-0.0073	0.0374	0.691	0.0722

WCR-the proposed nonparametric WCR method;
Obuchowski-Obuchowski's nonparametric method for clustered ROC data;
Nonparametric-the nonparametric ROC method for independent ROC data;
RMSE-square root of mean squared error;
CP-coverage percentage of 95% confidence intervals;
Length- the average length of the 95% confidence intervals.

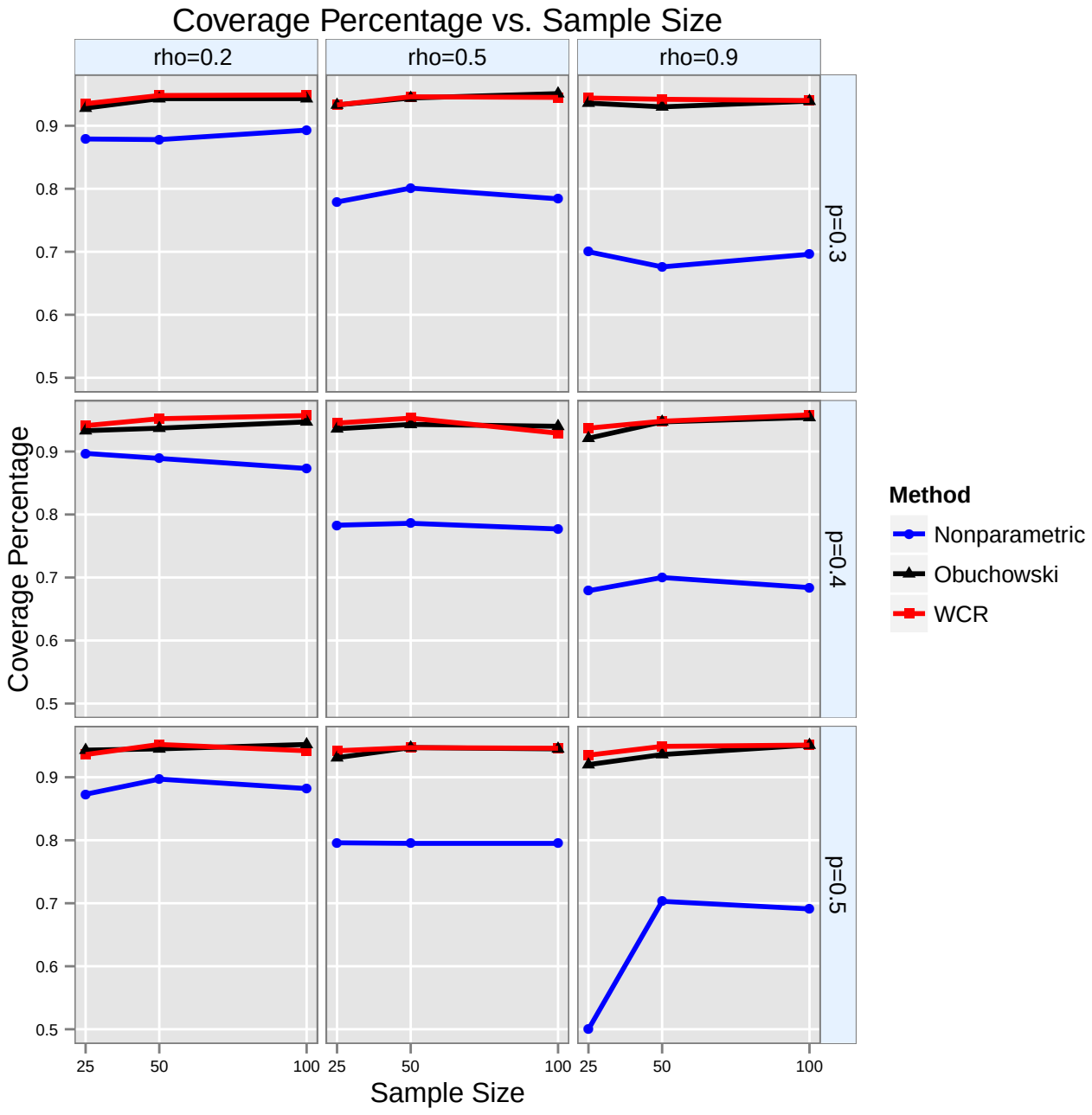

Figure 2.5: The coverage percentage of the 95% confidence intervals of the traditional nonparametric method, Obuchowski's nonparametric method and proposed nonparametric WCR method for lognormal clustered ROC data

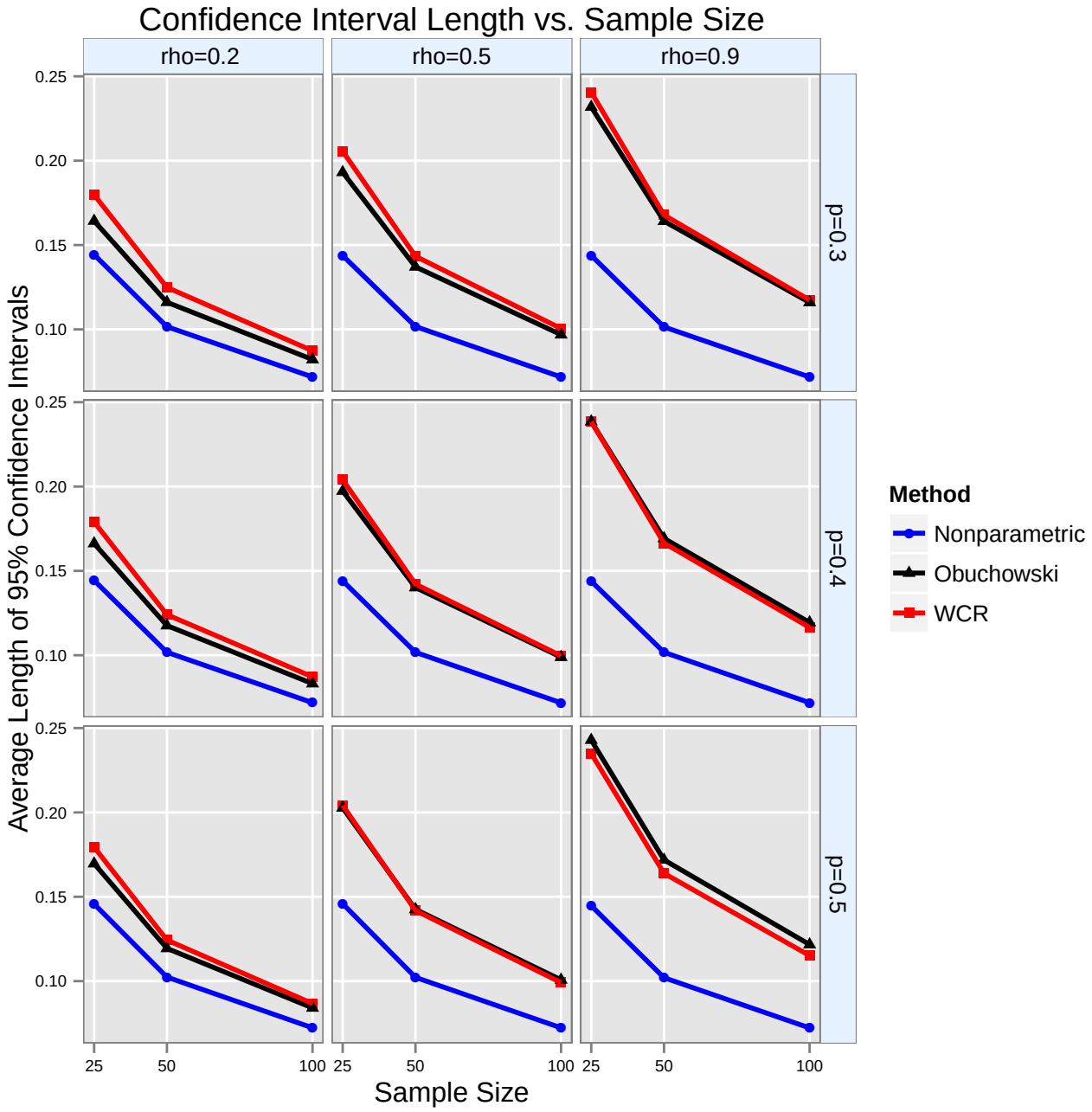

Figure 2.6: The average length of the 95% confidence intervals of the traditional nonparametric method, Obuchowski's nonparametric method and proposed nonparametric WCR methods for log-normal clustered ROC data

We also plot the empirical ROC curve for each simulated data. We calculated the averages of the standard deviation of the adjoint point difference of the empirical WCR ROC curves and the empirical curves.

The simulation settings are similar as Section 2.2.1. Let I_1 and I_0 denote the number of clusters in the diseased group and the nondiseased group. We let the two groups have the same number of clusters, so that $I_1 = I_0 = I/2$. The clusters in the diseased group have a cluster size $m_i = 3$ with probability p and a cluster size $m_i = 6$ with probability $1 - p$, where as the clusters in the nondiseased group have a cluster size $n_j = 2$ with probability $1 - p$ and a cluster size $n_j = 5$ with probability p. We simulate clustered continuous ROC data from normal and lognormal distributions:

1. $T^d \sim N(\mu_{T^d}, \mathbf{\Sigma}_{T^d})$ and $T^{\bar{d}} \sim N(\mu_{T^{\bar{d}}}, \mathbf{\Sigma}_{T^{\bar{d}}})$, where $\boldsymbol{\mu}_{T^d} = (1, 1, 0)$ when $m_i = 3$ and $\boldsymbol{\mu}_{T^d} = (1, 1, 1, 1, 1, 0)$ when $m_i = 6$, $\boldsymbol{\mu}_{T^{\bar{d}}} = (0, 0)$ when $n_j = 2$ and $\boldsymbol{\mu}_{T^{\bar{d}}} = (0, 0, 0, 0, 0)$ when $n_j = 5$. The variance-covariance matrix $\mathbf{\Sigma}_{T^d}$ is a $m_i \times m_i$ matrix with diagonal elements equal to 1 and correlation coefficients equal to ρ and $\mathbf{\Sigma}_{T^{\bar{d}}}$ is a $n_j \times n_j$ matrix with diagonal elements equal to 1 and correlation coefficients equal to ρ

2. $T^d \sim LogNormal(\mu_{T^d}, \mathbf{\Sigma}_{T^d})$ and $T^{\bar{d}} \sim LogNormal(\mu_{T^{\bar{d}}}, \mathbf{\Sigma}_{T^{\bar{d}}})$, with the same settings on μ_{T^d}, $\mathbf{\Sigma}_{T^d}$, $\mu_{T^{\bar{d}}}$, $\mathbf{\Sigma}_{T^{\bar{d}}}$, m_i, n_j and ρ.

After we generate clustered continuous ROC data, we round the data to no decimal. So that we have clustered ordinal data. We consider the informative cluster size correlation p of 0.3, 0.4 and 0.5. Note that when $p \neq 0.5$, the cluster size is different between the two groups. Under each setting, we consider the within-cluster correlation ρ of 0.2, 0.5, 0.9 and number of clusters in each group $I/2$ of 25, 50 and 100.

For the simulated clustered ordinal ROC data, we employ the proposed nonparametric WCR methods, as well as traditional nonparametric method. We obtain the averages of the standard deviation of the adjoint point difference of the empirical WCR ROC curves and the empirical curves.

In Tables 2.5 and 2.6, the averages of the adjoint point difference of the first derivatives of the empirical WCR ROC curves are smaller than those from the empirical curves. It means that the

nonparametric WCR methods can estimate a smoother ROC curve than the traditional nonparametric method for clustered ordinal data. We can estimate more accurate ROC summary measures, including the pAUC and the TPR at a fixed FPR if the ROC curve is smoother.

In Figures 2.7, and 2.8, we visualize the ROC curves by simulated clustered ordinal ROC data under two simulation settings. Figure 2.7 is under simulation setting one where we let $n = 50$, $p = 0.3$, $\rho = 0.2$. Figure 2.8 is under simulation setting two where we let $n = 50$, $p = 0.3$, $\rho = 0.9$. In both figures, the top left panel shows five empirical ROC curves and five empirical WCR ROC curves. The top right panel shows the averaged empirical ROC curve and averaged empirical WCR ROC curve. The bottom right panel shows ten empirical ROC curves and ten empirical WCR ROC curves. The bottom right panel shows the averaged empirical ROC curve and averaged empirical WCR ROC curve. It is obvious that the empirical WCR ROC curves are smoother. The averaged curves become smoother when the number of simulation becomes larger.

2.3 Data example

An motivating example is the eye exam data in the Sorbinil Retinopathy trial (Rosner, Glynn, and Lee 2003). Patients in the trial were randomized into three groups: each eye of the patients received the same treatment with an active drug in Group 1; both eyes of the patients received the same treatment with a placebo in Group 2; both eyes of each patient received the placebo and the other eye received the active drug in Group 3. The itching scores were measured at the third visit, which were from 0 (no itch at all) to 4 (severe itch) in an increments of 0.5. The resulting data are clustered with a fixed cluster size two. The number of itching scores that are from active drug treatment can be zero, one or two.

Another example is in the detection of glaucomatous deterioration. In order to detect visual field deterioration in glaucoma patients, Jiang developed a Bayesian hierarchical modeling method to predict the probability of the early diagnosis of glaucomatous progression using longitudinal visual field image data. The patients can either have none, one or two abnormal eye ratings. This generates the clustered data with cluster size two.

We now apply the procedure described in Section 2.1.2 with the example data sets from the

Table 2.5: Simulation results for normal clustered ordinal ROC data using two nonparametric methods

p	ρ	n	WCR SD of APD	Empirical SD of APD
0.3	0.2	25	0.0328	0.1552
		50	0.0259	0.1498
		100	0.0247	0.1486
	0.5	25	0.0328	0.1561
		50	0.0268	0.1520
		100	0.0251	0.1485
	0.9	25	0.0364	0.1628
		50	0.0309	0.1531
		100	0.0281	0.1501
0.4	0.2	25	0.0326	0.1535
		50	0.0251	0.1515
		100	0.0241	0.1485
	0.5	25	0.0342	0.1570
		50	0.0263	0.1518
		100	0.0245	0.1500
	0.9	25	0.0365	0.1634
		50	0.0306	0.1554
		100	0.0273	0.1502
0.5	0.2	25	0.0319	0.1547
		50	0.0249	0.1506
		100	0.0234	0.1480
	0.5	25	0.0335	0.1582
		50	0.0265	0.1525
		100	0.0252	0.1495
	0.9	25	0.0354	0.1631
		50	0.0301	0.1558
		100	0.0284	0.1514

WCR-the proposed nonparametric WCR method;
Empirical-the nonparametric ROC method for independent ROC data;
SD of APD - the average of standard deviation of the adjoint point difference of the ROC curve.

Table 2.6: Simulation results for lognormal clustered ordinal ROC data using two nonparametric methods

p	ρ	n	WCR SD of APD	Empirical SD of APD
0.3	0.2	25	0.0198	0.0733
		50	0.0149	0.0662
		100	0.0148	0.0587
	0.5	25	0.0207	0.0735
		50	0.0153	0.0660
		100	0.0153	0.0598
	0.9	25	0.0222	0.0810
		50	0.0170	0.0715
		100	0.0168	0.0649
0.4	0.2	25	0.0195	0.0742
		50	0.0148	0.0662
		100	0.0147	0.0601
	0.5	25	0.0198	0.0744
		50	0.0151	0.0688
		100	0.0152	0.0597
	0.9	25	0.0214	0.0823
		50	0.0168	0.0728
		100	0.0167	0.0645
0.5	0.2	25	0.0193	0.0738
		50	0.0146	0.0661
		100	0.0146	0.0597
	0.5	25	0.0193	0.0756
		50	0.0149	0.0670
		100	0.0151	0.0604
	0.9	25	0.0211	0.0806
		50	0.0166	0.0721
		100	0.0166	0.0649

WCR-the proposed nonparametric WCR method;
Empirical-the nonparametric ROC method for independent ROC data;
SD of APD - the average of standard deviation of the adjoint point difference of the ROC curve.

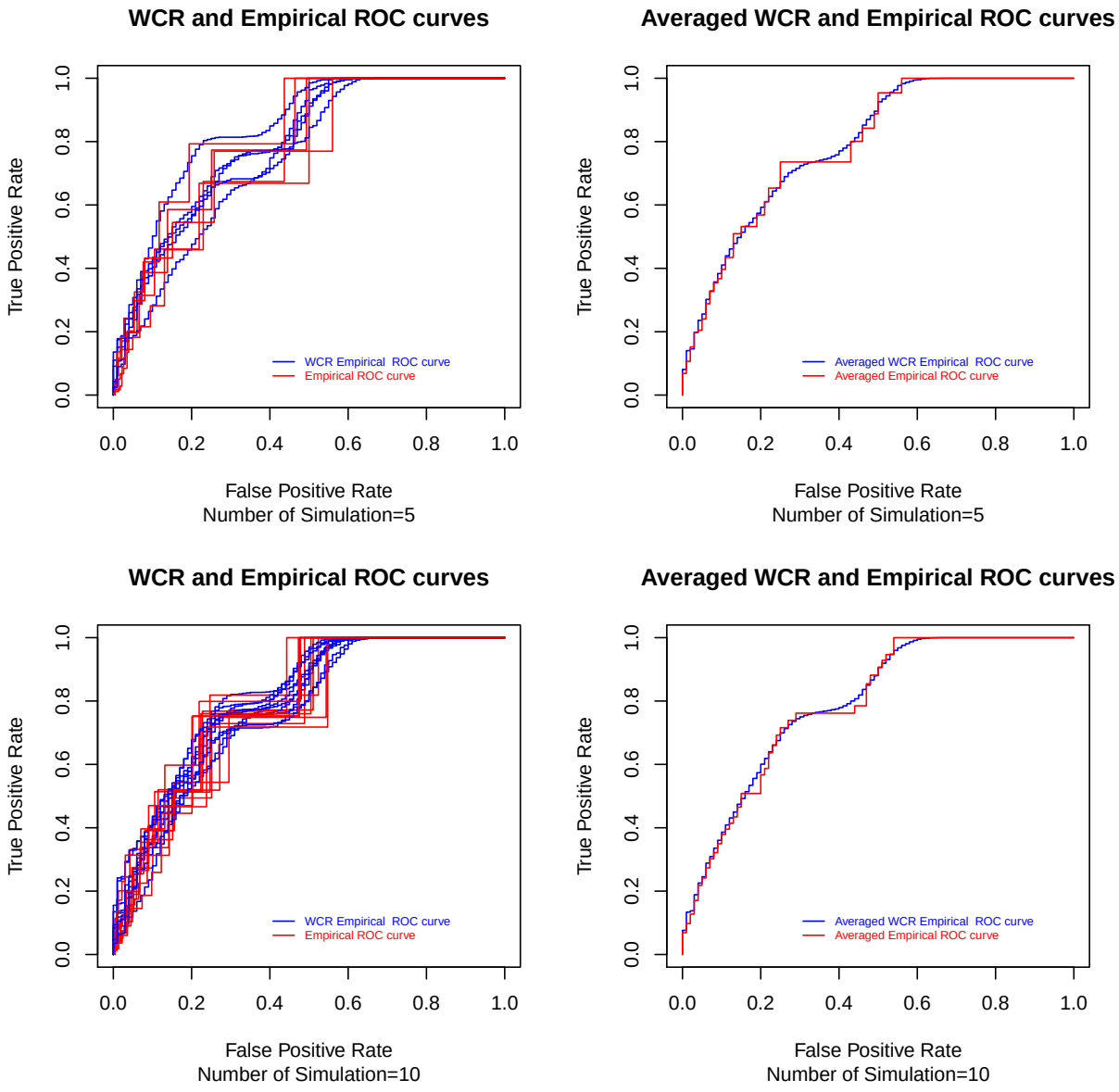

Figure 2.7: Comparison of the empirical WCR ROC curves and empirical ROC curves under the first setting, where $n = 50$, $p = 0.3$, $\rho = 0.2$

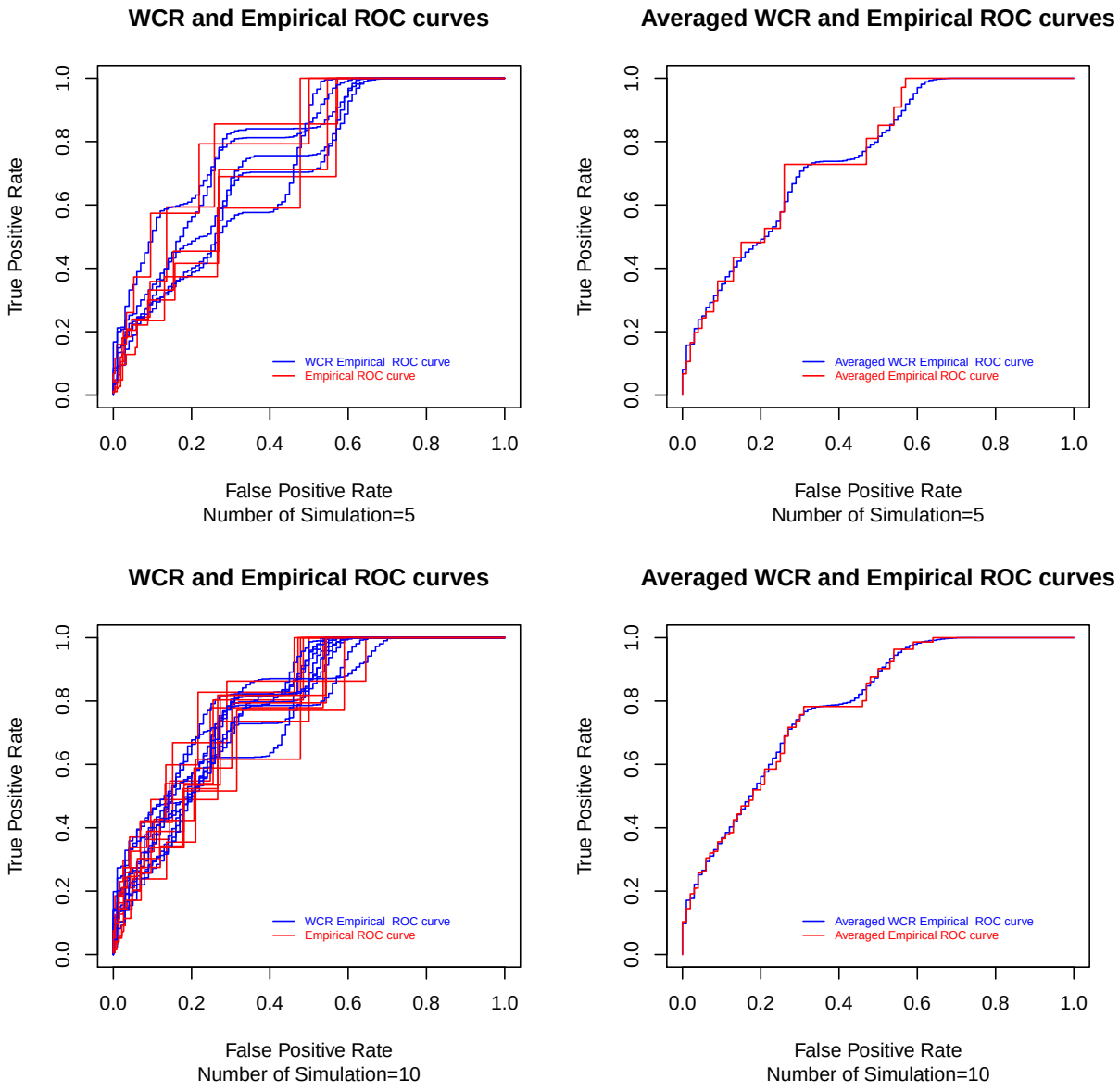

Figure 2.8: Comparison of the empirical WCR ROC curves and empirical ROC curves under the second setting, where $n = 50$, $p = 0.3$, $\rho = 0.9$

Sorbinil Retinopathy trial and the detection of glaucomatous deterioration. Table 2.7 gives the AUC, the variance and 95% confidence interval estimates using the Sorbinil Retinopathy trial data set. Compared to Rosner's Wilcoxon rank sum test, the WCR method and Obuchowski's method give similar AUC, variance and 95% confidence interval estimates. Their estimated 95% confidence intervals are larger than 0.5, which means that the biomarker has some diagnostic accuracy. Li and Zhou's method gives a smaller AUC estimate, and a larger variance. For the estimated 95% confidence interval, the lower bound is smaller than the lower bound by other methods, and the upper bound is similar to the upper bounds estimated by other methods. Since the interval covers 0.5, the biomarker might not have good diagnostic accuracy. Li's method did not perform well on this data set because the scores are ordinal and Li's method does not adjust for ties while the other three methods can handle with ties.

Table 2.7: Comparison of WCR method and other methods for the first data example

Methods	AUC	var(AUC)	95% confidence interval
Rosner	0.6283	0.00334	(0.5150, 0.7416)
Obuchowski	0.6283	0.00259	(0.5286, 0.7280)
Li&Zhou	0.5304	0.01015	(0.3329, 0.7279)
WCR	0.6277	0.00283	(0.5234, 0.7320)

Figure 2.9 shows that, compared to the empirical method, the WCR method gives a smoother ROC curve since we can estimate the WCR ROC curve by connecting all the WCR true positive rates, which can be estimated by averaging all the resampled true positive rates at the corresponding false positive rates. In the figure, we choose 20 false positive rates; correspondingly, there are 20 WCR true positive rates. The ROC curve would be smoother if we choose more false positive rates.

Table 2.8 gives the AUC, the AUC variance and 95% confidence interval estimates using detection of glaucomatous deterioration data set by Li and Zhou's method, Obuchowski's method and WCR method. They give similar AUC estimates since the data are continuous. Since there are some ties, Li and Zhou's method gives a slightly smaller AUC estimate. But Li's method gives larger variance, which leads to a bigger 95% confidence interval. The other two methods give similar confidence intervals, which are larger than 0.5 and indicate a good diagnostic accuracy of the biomarker.

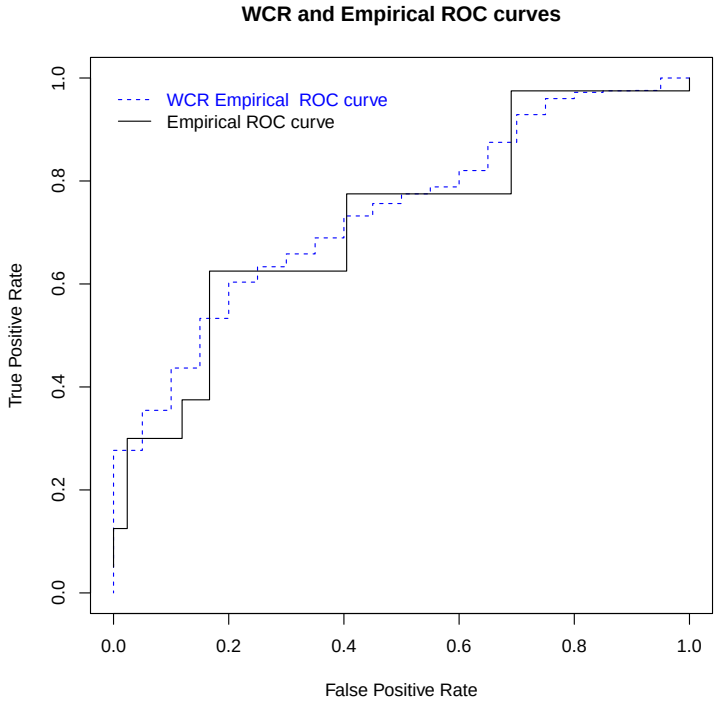

Figure 2.9: WCR empirical ROC curve and empirical ROC curve for the first data example

Table 2.8: Comparison of WCR method and other methods for the second data example

Methods	AUC	var(AUC)	95% confidence interval
Li&Zhou	0.9442	0.00226	(0.8510, 1.0373)
Obuchowski	0.9602	0.00018	(0.9339, 0.9865)
WCR	0.9566	0.00023	(0.9269, 0.9863)

Figure 2.10 shows that, compared to the empirical method, the WCR method gives a smoother ROC curve. The more false positive rates we choose, the smoother the ROC can be. Since the biomarker has high diagnostic accuracy, the ROC curve is close to the upper left and the AUC is close to one.

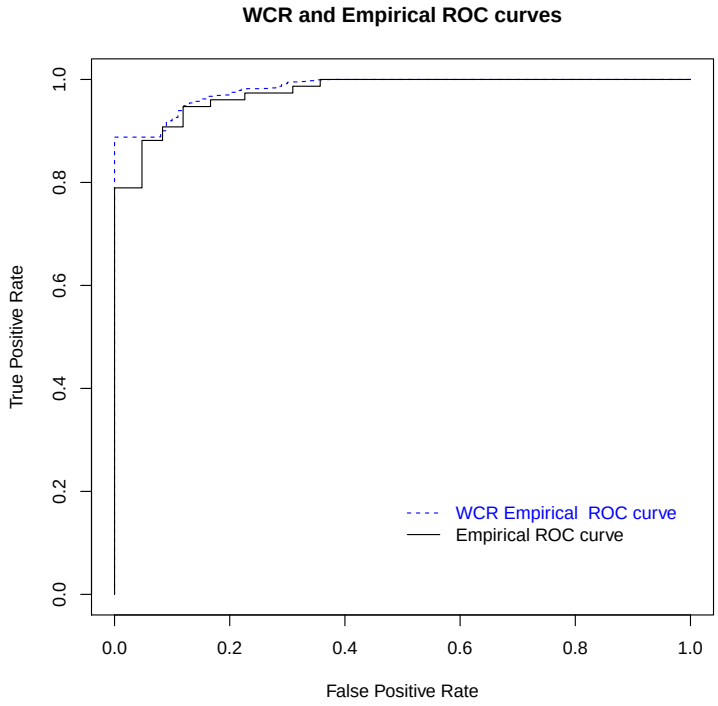

Figure 2.10: WCR empirical ROC curve and empirical ROC curve for the second data example

Chapter 3: Within Cluster Resampling (WCR) Methods for Two ROC Curve

3.1 Comparing Two Biomarkers

The within cluster resampling method for comparison of cluster ROC data of two biomarker is proposed. Let $T^{d}_{\ell ij}$ denote the jth continuous case result of ℓth biomarker in ith cluster, where $i = 1, \ldots, I$, $j = 1, \ldots, m_{\ell i}$, and $\ell = 1, 2$. Let $T^{\bar{d}}_{\ell ik}$ denotes the kth continuous control result of ℓth biomarker in ith cluster, where $k = 1, \ldots, n_{\ell i}$. The total number of case results of ℓth biomarker in all clusters is $M_\ell = \sum_{i=1}^{I} m_{\ell i}$, and the total number of control results of lth biomarker in all clusters is $N_\ell = \sum_{i=1}^{I} n_{\ell i}$. For each cluster, there are case and control results of the ℓth biomarker. For the ℓth biomarker, the cluster size is $n_{\ell i} + m_{\ell i}$, which is the number of observation of the lth biomarker in ith cluster.

To compare the areas under two ROC curves, we first apply the within cluster resampling to the clustered ROC data of each biomarker. Then we apply the ROC methods of independent data to the resampled data and average the resampled results. For the qth resample, we randomly select one biomarker result of the ℓth biomarker, where $\ell = 1, 2$, out of $n_{\ell i} + m_{\ell i}$ from the ith cluster, and denote the selected observation $T^{*}_{\ell i,q}$, which could either be a case or a control. To develop some notation, we rearrange the resampled $T^{*}_{\ell i,q}$ so that the first $d_{\ell q}$ observations are case biomarker results, denoted as $T^{d*}_{\ell i_1,q}, i_1 = 1 \ldots d_{\ell q}$, and the rest of the observations are control biomarker results, denoted as $Y^{*}_{\ell i_2,q}, i_2 = d_{\ell q}+1, \ldots, I$. The two ROC curves and the difference of AUCs could be obtained from the qth resampled dataset $(\mathbf{T}^{d*}_{\ell i_1,q}, \mathbf{T}^{\bar{d}*}_{\ell i_2,q})$ by either parametric, nonparametric or semiparametric ROC methods. Assume $T^{d*}_{\ell i_1,q}$ follows distribution F_ℓ and $T^{\bar{d}*}_{\ell i_2,q}$ follows distribution

G_ℓ. The ROC curves are

$$\widehat{ROC}^*_{\ell q}(u) = 1 - \hat{F}^*_{\ell q}(\hat{G}^{*}_{\ell q}{}^{-1}(1-u)), \tag{3.1}$$

and the corresponding difference of wAUCs is

$$\hat{\Delta}^*_q = \widehat{wAUC}^*_{1q} - \widehat{wAUC}^*_{2q} = \int_0^1 \widehat{ROC}^*_{\ell q}(u)dW(u) - \int_0^1 \widehat{ROC}^*_{2q}(u)dW(u). \tag{3.2}$$

Denote $\widehat{ROC}^*_{\ell q}$ the ROC curve estimated from the qth resampled dataset and $\widehat{wAUC}^*_{\ell q}$ and $\hat{\Delta}^*_q$ the estimated qth wAUCs and the estimated difference of two wAUCs. Hence the WCR difference of wAUCs estimator is estimated by

$$\hat{\Delta}_{WCR} = \frac{1}{Q}\sum_{q=1}^{Q}\hat{\Delta}^*_q. \tag{3.3}$$

The variance is estimated by

$$\hat{\Delta}_{WCR} = \frac{1}{Q}\sum_{q=1}^{Q}\hat{\Delta}^*_q, \tag{3.4}$$

$$\widehat{var}(\hat{\Delta}_{WCR}) = \frac{1}{Q}\sum_{q=1}^{Q}\widehat{var}(\hat{\Delta}^*_q) - S^2_\Delta, \tag{3.5}$$

where

$$S^2_\Delta = \frac{1}{Q-1}\sum_{q=1}^{Q}(\hat{\Delta}^*_q - \hat{\Delta}_{WCR})^2, \tag{3.6}$$

is the variability of the resampled $\hat{\Delta}^*_q$ estimators.

Table 3.1 gives the major steps of within cluster resampling method on cluster ROC data

Table 3.1: Schematic representation of WCR ROC methods on comparing two biomarkers

	$\mathbf{T}_\ell^d, \mathbf{T}_\ell^d$				
	$\downarrow$				
1	$\mathbf{T}^{d*}_{\ell i_1,1}, \mathbf{T}^{\bar{d}*}_{\ell i_2,1}$	$\rightarrow$	$\widehat{ROC}^*_{\ell 1}(u)$	$\rightarrow$	$\widehat{\Delta}^*_1, \widehat{var}(\widehat{\Delta}^*_1)$
2	$\mathbf{T}^{d*}_{\ell i_1,2}, \mathbf{T}^{\bar{d}*}_{\ell i_2,2}$	$\rightarrow$	$\widehat{ROC}^*_{\ell 2}(u)$	$\rightarrow$	$\widehat{\Delta}^*_2, \widehat{var}(\widehat{\Delta}^*_2)$
$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$
Q	$\mathbf{T}^{d*}_{\ell i_1,Q}, \mathbf{T}^{\bar{d}*}_{\ell i_2,Q}$	$\rightarrow$	$\widehat{ROC}^*_{\ell Q}(u)$	$\rightarrow$	$\widehat{\Delta}^*_Q, \widehat{var}(\widehat{\Delta}^*_Q)$
					$\Downarrow$
					$\widehat{\Delta}_{WCR}, \widehat{var}(\widehat{\Delta}_{WCR}), S^2_\Delta$

3.1.1 Parametric WCR Methods

If we assume normal distribution, for the qth resampled dataset, the case and control results of the first biomarker follow a normal distribution $N(\mu_{1,D}, \sigma^2_{1,D})$ and $N(\mu_{1,\bar{D}}, \sigma^2_{1,\bar{D}})$,the case and control results of the second biomarker follow a normal distribution $N(\mu_{2,D}, \sigma^2_{2,D})$ and $N(\mu_{2,\bar{D}}, \sigma^2_{2,\bar{D}})$. There are two approach to estimate the WCR difference of AUCs. In the first approach, we first estimate the parameters a and b from qth resampled dataset by $\hat{a}^*_{\ell q} = (\hat{\mu}_{\ell q,D} - \hat{\mu}_{\ell q,\bar{D}})/\hat{\sigma}_{\ell q,D}$, $\hat{b}^*_{\ell q} = (\hat{\sigma}_{\ell q,\bar{D}})/\hat{\sigma}_{\ell q,D}$, where $\hat{\mu}_{\ell q,D} = \sum_{i_1=1}^{d_q} T^{d*}_{\ell i_1,q}/d_{\ell q}$, $\hat{\mu}_{\ell q,\bar{D}} = \sum_{i_2=d_q+1}^{I} T^{\bar{d}*}_{\ell i_2,q}/(I-d_{\ell q})$, $\hat{\sigma}^2_{\ell q,D} = \sum_{i_1=1}^{d_q}(T^{d*}_{\ell i_1,q} - \hat{\mu}_{\ell q,D})/(d_{\ell q}-1)$, $\hat{\sigma}^2_{\ell q,\bar{D}} = \sum_{i_2=d_q}^{I}(T^{\bar{d}*}_{\ell i_2,q} - \hat{\mu}_{\ell q,\bar{D}})/(I-d_{\ell q}-1)$ are the sample means and variances of resampled case and control results for the ℓth biomarker. The variance-covariance estimate of $\hat{a}^*_q$ and $\hat{b}^*_q$, are estimated by the following equations, $\widehat{var}(\hat{a}^*_{\ell q}) = (d_{\ell q}(\hat{a}^{*2}_{\ell q} + 2) + 2(I - d_{\ell q})\hat{b}^{*2}_{\ell q})/(2d_{\ell q}(I-d_{\ell q}))$, $\widehat{var}(\hat{b}^*_{\ell q}) = I\hat{b}^{*2}_{\ell q}/(2d_{\ell q}(I-d_{\ell q}))$ and $\widehat{cov}(\hat{a}^*_{\ell q}, \hat{b}^*_{\ell q}) = \hat{a}^*_{\ell q}\hat{b}^*_{\ell q}/(2(I-d_{\ell q}))$.

The ROC curves estimated from the qth resampled dataset are

$$\widehat{ROC}^*_{\ell q,BN} = \Phi(\hat{a}^*_{\ell q} + \hat{b}^*_{\ell q}\Phi^{-1}(u)), \tag{3.7}$$

Then we estimate the difference of AUCs, $\hat{\Delta}^{A*}_{q,BN}$, from the qth resampled dataset by

$$\hat{\Delta}^{A*}_{q,BN} = A\hat{U}C^{*}_{1q,BN} - A\hat{U}C^{*}_{2q,BN} = \Phi\left(\frac{\hat{a}^{*}_{1q}}{\sqrt{1+\hat{b}^{*}_{1q}{}^{2}}}\right) - \Phi\left(\frac{\hat{a}^{*}_{2q}}{\sqrt{1+\hat{b}^{*}_{2q}{}^{2}}}\right). \tag{3.8}$$

The variance of $\hat{\Delta}^{A*}_{q,BN}$ can be expressed in the following form,

$$var(\hat{\Delta}^{A*}_{q,BN}) = var(A\hat{U}C^{*}_{1q,BN}) + var(A\hat{U}C^{*}_{2q,BN}) - 2cov(A\hat{U}C^{*}_{1q,BN}, A\hat{U}C^{*}_{2q,BN}), \tag{3.9}$$

where

$$\widehat{var}(\widehat{AUC}^{*}_{\ell q}) = \hat{f}^{*2}_{\ell q}\widehat{var}(\hat{a}^{*}_{\ell q}) + \hat{g}^{*2}_{\ell q}\widehat{var}(\hat{b}^{*}_{\ell q}) + 2\hat{f}^{*}_{\ell q}\hat{g}^{*}_{\ell q}\widehat{cov}(\hat{a}^{*}_{\ell q}, \hat{b}^{*}_{\ell q}), \tag{3.10}$$

$$\begin{aligned}\widehat{cov}(\widehat{AUC}^{*}_{1q,BN}, \widehat{AUC}^{*}_{2q,BN}) =& \hat{f}^{*}_{1q}\hat{f}^{*}_{2q}\widehat{cov}(\hat{a}^{*}_{1q}, \hat{a}^{*}_{2q}) + \hat{g}^{*}_{1q}\hat{g}^{*}_{2q}\widehat{cov}(\hat{b}^{*}_{1q}, \hat{b}^{*}_{2q}) \\ &+ \hat{g}^{*}_{1q}\hat{f}^{*}_{2q}\widehat{cov}(\hat{b}^{*}_{1q}, \hat{a}^{*}_{2q}) + \hat{f}^{*}_{1q}\hat{g}^{*}_{2q}\widehat{cov}(\hat{a}^{*}_{1q}, \hat{b}^{*}_{2q}),\end{aligned} \tag{3.11}$$

with

$$\hat{f}^{*}_{\ell q} = \frac{e^{-\hat{a}^{*2}_{\ell q}/2(1+\hat{b}^{*2}_{\ell q})}}{\sqrt{2\pi(1+\hat{b}^{*2}_{\ell q})}},$$

$$\hat{g}^{*}_{\ell q} = \frac{\hat{a}^{*}_{\ell q}\hat{b}^{*}_{\ell q}e^{-\hat{a}^{*2}_{\ell q}/2(1+\hat{b}^{*2}_{\ell q})}}{\sqrt{2\pi(1+\hat{b}^{*2}_{\ell q})^{3}}},$$

$$\widehat{cov}(\hat{a}^{*}_{1q}, \hat{a}^{*}_{2q}) = \frac{I-d_q}{d_q^2} + \frac{\hat{b}^{*}_{1q}\hat{b}^{*}_{2q}}{d_q} + \frac{(I-d_q)\hat{a}^{*}_{1q}\hat{a}^{*}_{2q}}{2d_q^2},$$

$$\widehat{cov}(\hat{b}^{*}_{1q}, \hat{b}^{*}_{2q}) = \frac{\hat{b}^{*}_{1q}\hat{b}^{*}_{2q}(1+(I-d_q)/d_q)}{2d_q},$$

$$\widehat{cov}(\hat{a}^*_{1q}, \hat{b}^*_{2q}) = \frac{(I - d_q)\hat{a}^*_{1q}\hat{b}^*_{2q}}{2d_q^2},$$

and

$$\widehat{cov}(\hat{a}^*_{2q}, \hat{b}^*_{1q}) = \frac{(I - d_q)\hat{a}^*_{2q}\hat{b}^*_{1q}}{2d_q^2}.$$

The WCR difference of AUCs estimator is the average of all the resampled difference of AUCs, which is estimated by

$$\hat{\Delta}^A_{WCR,BN} = \frac{1}{Q}\sum_{q=1}^{Q}\hat{\Delta}^{A*}_{q,BN}. \tag{3.12}$$

The variance is estimated by

$$\widehat{var}(\hat{\Delta}^A_{WCR,BN}) = \frac{1}{Q}\sum_{q=1}^{Q}\widehat{var}(\hat{\Delta}^{A*}_{q,BN}) - S^2_{\Delta^A}, \tag{3.13}$$

where

$$S^2_{\Delta^A} = \frac{1}{Q-1}\sum_{q=1}^{Q}(\hat{\Delta}^{A*}_{q,BN} - \hat{\Delta}^A_{WCR,BN})^2, \tag{3.14}$$

is the variability of the resampled $\hat{\Delta}^{A*}_{q,BN}$.

3.1.2 Nonparametric WCR Methods

We could also use the empirical method to fit the ROC curve for the qth resampled dataset. The difference of AUCs could then be obtained by Delong's method (DeLong, DeLong, and Clarke-Pearson 1988) using Equation (1.37). For the qth resampled dataset $(\mathbf{T}^{d*}_{i_1,q}, \mathbf{T}^{\bar{d}*}_{i_2,q})$, the estimated ROC curve is

$$\widehat{ROC}^*_{\ell q,EM} = \frac{1}{d_{\ell q}}\sum_{i_1}^{d_{\ell q}} I[T^{d*}_{\ell i_1,q} > (1-u)\text{th percentile of } \{T^{\bar{d}*}_{\ell i_2,q}\}, i_2 = 1,\ldots,I-d_{\ell q}]. \tag{3.15}$$

The qth difference of AUCs is given by

$$\hat{\Delta}^{A*}_{q,DL} = \frac{1}{d_{1q}(I-d_{1q})}\sum_{i_1=1}^{d_{1q}}\sum_{i_2=d_{1q}+1}^{I}\Psi(T^{d*}_{1i_1,q},T^{\bar{d}*}_{1i_2,q}) - \frac{1}{d_{2q}(I-d_{2q})}\sum_{i_1=1}^{d_{2q}}\sum_{i_2=d_{2q}+1}^{I}\Psi(T^{d*}_{2i_1,q},T^{\bar{d}*}_{2i_2,q}), \tag{3.16}$$

where

$$\Psi(T^{d*}_{\ell i_1,q},T^{\bar{d}*}_{\ell i_2,q}) = \begin{cases} 1, & T^{d*}_{\ell i_1,q} > T^{\bar{d}*}_{\ell i_2,q} \\ \frac{1}{2}, & T^{d*}_{\ell i_1,q} = T^{\bar{d}*}_{\ell i_2,q} \\ 0, & T^{d*}_{\ell i_1,q} < T^{\bar{d}*}_{\ell i_2,q} \end{cases}. \tag{3.17}$$

The variance of $\hat{\Delta}^{A*}_{q,DL}$ is estimated by

$$\hat{\Delta}^{A*}_{q,DL} = v^{q,DL}_x/d_{1q} + v^{q,DL}_y/(I-d_{1q}), \tag{3.18}$$

where $v^{q,DL}_x$ and $v^{q,DL}_y$ are

$$\begin{aligned} v^{q,DL}_x = & \frac{1}{d_{1q}-1}\sum_{i_1=1}^{d_{1q}}\Bigg\{\left[\frac{1}{I-d_{1q}-1}\sum_{i_2=1}^{I-d_{1q}-1}\psi - \widehat{AUC}_{1,DL}\right]^2 + \left[\frac{1}{I-d_{1q}-1}\sum_{i_2=1}^{I-d_{1q}-1}\psi - \widehat{AUC}_{2,DL}\right]^2 \\ & - 2\left[\frac{1}{I-d_{1q}-1}\sum_{i_2=1}^{I-d_{1q}-1}\psi - \widehat{AUC}_{1,DL}\right]\left[\frac{1}{I-d_{1q}-1}\sum_{i_2=1}^{I-d_{1q}-1}\psi - \widehat{AUC}_{2,DL}\right]\Bigg\}, \end{aligned} \tag{3.19}$$

$$v_y^{q,DL} = \frac{1}{I - d_{1q} - 1} \sum_{j=1}^{I-d_{1q}} \left\{ \left[\frac{1}{d_{1q}} \sum_{i_1=1}^{d_{1q}} \psi - \widehat{AUC}_{1,DL} \right]^2 + \left[\frac{1}{d_{1q}} \sum_{i_1,q=1}^{d_{1q}} \psi - \widehat{AUC}_{2,DL} \right]^2 \right.$$
$$\left. - 2 \left[\frac{1}{d_{1q}} \sum_{i_1=1}^{d_{1q}} \psi - \widehat{AUC}_{1,DL} \right] \left[\frac{1}{d_{1q}} \sum_{i_1=1}^{d_{1q}} \psi - \widehat{AUC}_{2,DL} \right] \right\}, \tag{3.20}$$

where $\psi = \psi(T^d_{1i_1,q}, T^{\bar{d}}_{1i_2,q})$.

The WCR difference of AUCs estimator is given by

$$\hat{\Delta}^A_{WCR,DL} = \frac{1}{Q} \sum_{q=1}^{Q} \hat{\Delta}^{A*}_{q,DL}. \tag{3.21}$$

The variance is estimated by

$$\widehat{var}(\hat{\Delta}^A_{WCR,DL}) = \frac{1}{Q} \sum_{q=1}^{Q} \widehat{var}(\hat{\Delta}^{A*}_{q,DL}) - S^2_{\Delta^A}, \tag{3.22}$$

where

$$S^2_{\Delta^A} = \frac{1}{Q-1} \sum_{q=1}^{Q} (\hat{\Delta}^{A*}_{q,DL} - \hat{\Delta}^A_{WCR,DL})^2, \tag{3.23}$$

is the variability of the resampled $\hat{\Delta}^{A*}_{q,BN}$.

3.1.3 Semiparametric WCR Methods

The binary regression method (Pepe 2000) could be used to fit the ROC curve and estimate the difference of AUCs. For the qth resampling, the binary regression model in Equation (1.44) is

$$\widehat{ROC}_q^*(u) = g\{\sum_{\ell=1}^{2} \hat{\boldsymbol{\beta}}_{\ell q}^* h_{\ell q}(u)\} = g\{\hat{\beta}_{11,q}^* + \hat{\beta}_{12,q}^* h_q^{-1}(u) + \hat{\beta}_{21,q}^* I + \hat{\beta}_{22,q}^* I h_q^{-1}(u)\}, \quad (3.24)$$

where I is the indicator variable corresponding to the two biomarkers, with $I = 0$ when $\ell = 1$ and $I = 1$ when $\ell = 2$. The parameters $\boldsymbol{\beta}_{\ell q}^*$ could be estimated by GLM method (Pepe 2000) or LS method (**?**). Let $U_{i_1 i_2,q}^* = I[T_{i_1,q}^{d*} \geq T_{i_2,q}^{\bar{d}*}]$

$$\sum_{i_1=1}^{d_q} \sum_{i_2=1}^{I} \frac{U_{i_1 i_2,q}^* - g\{\Sigma_{\ell=1}^2 \boldsymbol{\beta}_{\ell q}^* h_{\ell q}(u_{i_2})\}}{g\{\Sigma_{\ell=1}^2 \boldsymbol{\beta}_{\ell q}^* h_{\ell q}(u_{i_2})\}(1 - g\{\Sigma_{\ell=1}^2 \boldsymbol{\beta}_{\ell q}^* h_{\ell q}(u_{i_2})\})} \frac{\partial g\{\Sigma_{\ell=1}^2 \boldsymbol{\beta}_{\ell q}^* h_{\ell q}(u_{i_2})\}}{\partial \boldsymbol{\beta}_{\ell q}^*} = 0 \quad (3.25)$$

Under the normal assumption, the AUC difference estimator is

$$\begin{aligned}\hat{\Delta}_{q,SM}^{A*} &= \int_0^1 \Phi\{\hat{\beta}_{11,q}^* + \hat{\beta}_{12,q}^* \Phi^{-1}(u)\} du - \int_0^1 \Phi\{\hat{\beta}_{11,q}^* + \hat{\beta}_{12,q}^* \Phi^{-1}(u) + \hat{\beta}_{21,q}^* + \hat{\beta}_{22,q}^* \Phi^{-1}(u)\} du \\ &= \Phi\left(\frac{\hat{\beta}_{11,q}^*}{\sqrt{1 + {\hat{\beta}_{12,q}^*}^2}}\right) - \Phi\left(\frac{\hat{\beta}_{11,q}^* + \hat{\beta}_{21,q}^*}{\sqrt{1 + (\hat{\beta}_{12,q}^* + \hat{\beta}_{22,q}^*)^2}}\right). \quad (3.26)\end{aligned}$$

Tang and Zhou (2009) derived the asymptotical properties for the aforementioned GLM method and LS method. For GLM estimator,

$$var(\Delta_{q,SM}^{A*}) = var(AUC_{1q}^*) + var(AUC_{2q}^*) - cov(AUC_{1q}^*, AUC_{2q}^*),$$

where

$$var(AUC_{1q}^*) = B_{1,q}^{*T} \Sigma_{11,q}^* B_{1,q}^*, \quad var(AUC_{2q}^{GLM}) = B_{2,q}^{*T} \Sigma_{22,q}^* B_{2,q}^*,$$

and

$$cov(AUC^*_{1q}, AUC^*_{2q}) = B^{*T}_{1,q}(\Sigma^*_{11,q} + \Sigma^*_{21,q})B^*_{2,q},$$

with

$$B^*_{1,q} = \{\phi\left(\frac{\hat{\beta}^*_{11,q}}{\sqrt{1+\hat{\beta}^{*2}_{12,q}}}\right)\frac{1}{\sqrt{1+\beta^{*2}_{12,q}}}, -\phi\left(\frac{\beta^*_{11,q}}{\sqrt{1+\beta^{*2}_{12,q}}}\right)\frac{\beta^*_{11,q}}{(\sqrt{1+\beta^{*2}_{12,q}})^{3/2}}\}^T,$$

$$B^*_{2,q} = \{\phi\left(\frac{\hat{\beta}^*_{11,q}+\hat{\beta}^*_{21,q}}{\sqrt{1+(\hat{\beta}^*_{12,q}+\hat{\beta}^*_{22,q})^2}}\right)\frac{1}{\sqrt{1+(\hat{\beta}^*_{12,q}+\hat{\beta}^*_{22,q})^2}},$$

$$-\phi\left(\frac{\hat{\beta}^*_{11,q}+\hat{\beta}^*_{21,q}}{\sqrt{1+(\hat{\beta}^*_{12,q}+\hat{\beta}^*_{22,q})^2}}\right)\frac{\hat{\beta}^*_{11,q}+\hat{\beta}^*_{21,q}}{(\sqrt{1+(\hat{\beta}^*_{12,q}+\hat{\beta}^*_{22,q})^2})^{3/2}}\}^T,$$

$$\Sigma^*_{11,q} = cov(\hat{\beta}^*_{11,q}, \hat{\beta}^*_{12,q}), \quad \Sigma^*_{22,q} = cov(\hat{\beta}^*_{21,q}, \hat{\beta}^*_{22,q}), \quad \Sigma^*_{21,q} = cov(\hat{\beta}^*_{12,q}, \hat{\beta}^*_{22,q}).$$

Here $\Sigma^*_{k\tilde{k},q}$ is the 2×2 submatrices of

$$\Sigma^*_q = \begin{pmatrix} \Sigma^*_{11,q}, \Sigma^*_{12,q} \\ \Sigma^*_{21,q}, \Sigma^*_{22,q} \end{pmatrix},$$

The WCR AUC difference can be obtained by averaging all $\hat{\Delta}^A_{q,SM}$,

$$\hat{\Delta}^A_{WCR,SM_1} = \frac{1}{Q}\sum_{q=1}^{Q}\hat{\Delta}^{A*}_{q,SM}. \tag{3.27}$$

The variance is estimated by

$$\widehat{var}(\hat{\Delta}^{A}_{WCR,SM_1}) = \frac{1}{Q}\sum_{q=1}^{Q}\widehat{var}(\hat{\Delta}^{A*}_{q,SM_1}) - S^2_{\Delta^A}, \tag{3.28}$$

where

$$S^2_{\Delta^A} = \frac{1}{Q-1}\sum_{q=1}^{Q}(\hat{\Delta}^{A*}_{q,SM_1} - \hat{\Delta}^{A}_{WCR,SM_1})^2, \tag{3.29}$$

is the variability of the resampled $\hat{\Delta}^{A*}_{q,BN}$.

Another approach to obtain the WCR AUC difference estimator is, first we estimate the parameters $\hat{\boldsymbol{\beta}}^{*}_{\ell q}$. Then we average the estimated parameter to get the WCR parameters $\hat{\boldsymbol{\beta}}_{\ell,WCR}$. Next we plug $\hat{\boldsymbol{\beta}}_{\ell,WCR}$ into Equation (1.44) and get $\hat{\Delta}^{A}_{WCR,SM_2}$, which is given by

$$\hat{\Delta}^{A}_{WCR,SM_2} = \Phi\left(\frac{\hat{\beta}_{11,WCR}}{\sqrt{1+\hat{\beta}^2_{12,WCR}}}\right) - \Phi\left(\frac{\hat{\beta}_{11,WCR}+\hat{\beta}_{21,WCR}}{\sqrt{1+(\hat{\beta}_{12,WCR}+\hat{\beta}_{22,WCR})^2}}\right). \tag{3.30}$$

3.2 Simulation Study

In this section, we report simulation studies to evaluate the performance of the proposed WCR methods. In particular, we are interested in whether the proposed methods can account for the within-cluster correlation and give us valid Δ^A and variance estimators. We focus primarily on the coverage percentage of the confidence interval estimated by the proposed methods. We perform our methods on the simulated clustered ROC data and estimate the WCR Δ^A and the WCR variance by the parametric WCR methods and the nonparametric WCR method. We compare our methods with the traditional methods and show the bias in using the traditional methods on clustered ROC data. We consider the situation where, there are two biomarkers within each subject, for a diseased subject, there are either 2 or 5 nondiseased results plus 1 diseased result for each biomarker, for a nondiseased subject, all biomarker results in the same cluster are normal for each biomarker.

Let $I_{\ell 1}$ and $I_{\ell 0}$ denote the number of clusters in the diseased group and the nondiseased group for the ℓth biomarker, and $I_{11} = I_{21}$, $I_{10} = I_{20}$. We let the two groups have the same number of clusters, so that $I_{\ell 1} = I_{\ell 0} = I/2$. For the ℓth biomarker, the clusters in the diseased group have a cluster size $m_{\ell i} = 3$ with probability p and a cluster size $m_{\ell i} = 6$ with probability $1 - p$, where as the clusters in the nondiseased group have a cluster size $n_{\ell j} = 2$ with probability $1 - p$ and a cluster size $n_{\ell j} = 5$ with probability p. We simulate 1000 clustered ROC data from normal and lognormal distributions, respectively:

1. $T_\ell^d \sim N(\mu_{T_\ell^d}, \mathbf{\Sigma}_{T_\ell^d})$ and $T_\ell^{\bar{d}} \sim N(\mu_{T_\ell^{\bar{d}}}, \mathbf{\Sigma}_{T_\ell^{\bar{d}}})$, where $\boldsymbol{\mu}_{T_1^d} = (1, 1, 0)$ and $\boldsymbol{\mu}_{T_2^d} = (0.7, 0.7, 0)$ when $m_{\ell i} = 3$ and $\boldsymbol{\mu}_{T_1^d} = (1, 1, 1, 1, 1, 0)$ and $\boldsymbol{\mu}_{T_2^d} = (0.7, 0.7, 0.7, 0.7, 0)$ when $m_{\ell i} = 6$, $\boldsymbol{\mu}_{T_\ell^{\bar{d}}} = (0, 0)$ when $n_{\ell j} = 2$ and $\boldsymbol{\mu}_{T_\ell^{\bar{d}}} = (0, 0, 0, 0, 0)$ when $n_{\ell j} = 5$. The variance-covariance matrix $\mathbf{\Sigma}_{T_\ell^d}$ is a $m_{\ell i} \times m_{\ell i}$ matrix with diagonal elements equal to 1 and correlation coefficients equal to ρ and $\mathbf{\Sigma}_{T_\ell^{\bar{d}}}$ is a $n_{\ell j} \times n_{\ell j}$ matrix with diagonal elements equal to 1 and correlation coefficients equal to ρ

2. $T_\ell^d \sim LogNormal(\mu_{T_\ell^d}, \mathbf{\Sigma}_{T_\ell^d})$ and $T_\ell^{\bar{d}} \sim LogNormal(\mu_{T_\ell^{\bar{d}}}, \mathbf{\Sigma}_{T_\ell^{\bar{d}}})$, with the same settings on $\mu_{T_\ell^d}$, $\mathbf{\Sigma}_{T_\ell^d}$, $\mu_{T_\ell^{\bar{d}}}$, $\mathbf{\Sigma}_{T_\ell^{\bar{d}}}$, $m_{\ell i}$, $n_{\ell j}$ and ρ.

We let p, the informative cluster size correlation, be 0.3, 0.4 and 0.5. Note that when $p \neq 0.5$, the cluster size is different between the two groups. Under each setting, we let ρ, the within-cluster correlation, be 0.2, 0.5, 0.9 and $I/2$, the number of clusters in each group, be 25, 50 and 100.

For the simulated normal clustered ROC data, we employ the proposed parametric WCR methods and nonparametric WCR method, as well as traditional parametric and nonparametric methods and Obuchowski's method. For the simulated lognormal clustered ROC data, we apply only nonparametric WCR method, traditional nonparametric method and Obuchowski's method. Li and Zhou's method gives the same estimator as Obuchowski's method, and is not compared in the simulation study. We obtain the AUC estimators and 95% confidence intervals from all the methods. Biases, square root of mean squared errors, and simulated coverage percentage of 95% confidence intervals under various scenarios are shown in the tables.

In Table 3.2 , we compare the proposed parametric WCR methods with the traditional parametric method when the data is normally distributed. In Table 3.3 and Table 3.4, we compare the proposed nonparametric WCR method, traditional nonparametric method (DeLong, DeLong, and Clarke-Pearson 1988), and Obuchowski's nonparametric method (Obuchowski 1997) using simulated normally and lognormal data. It is clear that the coverage percentages obtained by our methods are close to the nominal level and do not change as the within-cluster correlation becomes larger. Also the biases obtained by proposed methods are close to zero. This indicates that proposed WCR methods have a good performance on clustered ROC data and can account for the within-cluster correlation. On the contrary, the coverage percentages obtained by traditional methods are not close to 95% and as within-cluster correlation increases, the coverage percentages decreases. Our method handles the within-cluster correlation better than the traditional methods do. In Table 2.4, we compare the nonparametric WCR methods with the traditional nonparametric method when the normal assumption is violated. The WCR methods work well on lognormal data and obtain better coverage percentages than those from the traditional nonparametric method. The results obtained by WCR method and Obuchowski's method are similar, which indicate that the biomarker has similar accuracy on patients and locations.

In Figures, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6. we visualized the simulation results for the coverage percentage of the 95% confidence intervals and the average length of the 95% confidence intervals.

Table 3.2: Simulation results for normal clustered ROC data using three parametric methods

			WCR1				WCR2				Parametric			
p	ρ	n	Bias (%)	RMSE	CP	Length	Bias (%)	RMSE	CP	Length	Bias (%)	RMSE	CP	Length
0.3	0.2	25	0.1962	0.0445	0.937	0.1292	0.0259	0.0438	0.944	0.1715	-0.3692	0.0686	0.954	0.2792
		50	0.1742	0.0312	0.936	0.0928	0.0866	0.0310	0.945	0.1195	-0.1412	0.0490	0.927	0.1948
		100	-0.0616	0.0229	0.934	0.0666	-0.1055	0.0228	0.927	0.0843	-0.2049	0.0346	0.931	0.1385
	0.5	25	0.4155	0.0400	0.935	0.1228	0.2855	0.0394	0.952	0.1560	-0.2365	0.0580	0.921	0.2354
		50	-0.0289	0.0280	0.926	0.0837	-0.0952	0.0279	0.929	0.1065	0.0516	0.0400	0.896	0.1649
		100	-0.0949	0.0198	0.934	0.0598	-0.1277	0.0198	0.940	0.0752	-0.0485	0.0278	0.914	0.1161
	0.9	25	-0.0762	0.0343	0.933	0.1206	-0.1203	0.0341	0.938	0.1304	-0.2253	0.0279	0.827	0.1611
		50	-0.1195	0.0236	0.930	0.0860	-0.1422	0.0235	0.961	0.0921	-0.2019	0.0187	0.824	0.1110
		100	0.1379	0.0175	0.928	0.0606	0.1265	0.0175	0.938	0.0648	0.0126	0.0135	0.825	0.0773
0.4	0.2	25	0.1735	0.0442	0.930	0.1278	-0.0049	0.0436	0.949	0.1699	-0.0920	0.0765	0.945	0.3051
		50	0.1822	0.0319	0.932	0.0918	0.0937	0.0316	0.936	0.1192	0.1897	0.0536	0.943	0.2110
		100	0.0253	0.0218	0.941	0.0662	-0.0190	0.0217	0.945	0.0839	0.0072	0.0374	0.923	0.1490
	0.5	25	0.6662	0.0404	0.920	0.1200	0.5167	0.0396	0.937	0.1536	-0.2020	0.0590	0.912	0.2566
		50	0.0217	0.0283	0.941	0.0831	-0.0446	0.0281	0.930	0.1061	0.0043	0.0438	0.904	0.1791
		100	-0.0093	0.0199	0.923	0.0592	-0.0439	0.0199	0.932	0.0746	-0.0728	0.0301	0.901	0.0010
	0.9	25	-0.0520	0.0348	0.938	0.1190	-0.0992	0.0345	0.949	0.1288	-0.3950	0.0309	0.811	0.1742
		50	-0.1105	0.0242	0.916	0.0847	-0.1340	0.0241	0.934	0.0909	-0.2175	0.0203	0.814	0.0009
		100	0.0451	0.0176	0.944	0.0601	0.0330	0.0175	0.932	0.0644	-0.1024	0.0145	0.793	0.0838
0.5	0.2	25	0.2026	0.0438	0.938	0.1291	0.0270	0.0432	0.942	0.1711	-0.5119	0.0833	0.949	0.3315
		50	0.0736	0.0304	0.930	0.0916	-0.0161	0.0302	0.949	0.1187	0.0071	0.0610	0.937	0.2326
		100	-0.0127	0.0220	0.950	0.0657	-0.0560	0.0219	0.935	0.0835	-0.0814	0.0429	0.933	0.1629
	0.5	25	0.2696	0.0401	0.911	0.1191	0.1279	0.0395	0.936	0.1532	-0.1903	0.0700	0.898	0.2827
		50	0.1321	0.0288	0.925	0.0825	0.0622	0.0286	0.912	0.1054	-0.3207	0.0476	0.907	0.1967
		100	0.1870	0.0202	0.919	0.0585	0.1522	0.0201	0.930	0.0739	0.0010	0.0348	0.893	0.1379
	0.9	25	-0.2061	0.0331	0.933	0.1170	-0.2563	0.0329	0.934	0.1272	-0.5015	0.0337	0.789	0.1934
		50	-0.1290	0.0242	0.935	0.0838	-0.1540	0.0241	0.934	0.0901	-0.2124	0.0229	0.761	0.1325
		100	-0.0480	0.0173	0.939	0.0593	-0.0607	0.0172	0.931	0.0635	-0.1384	0.0161	0.772	0.0921

WCR-the proposed parametric WCR method proposed;
Parametric-the parametric ROC method for independent data;
RMSE-square root of mean squared error; Coverage-the coverage percentage of 95% confidence intervals;
Length- the average length of the 95% confidence intervals.

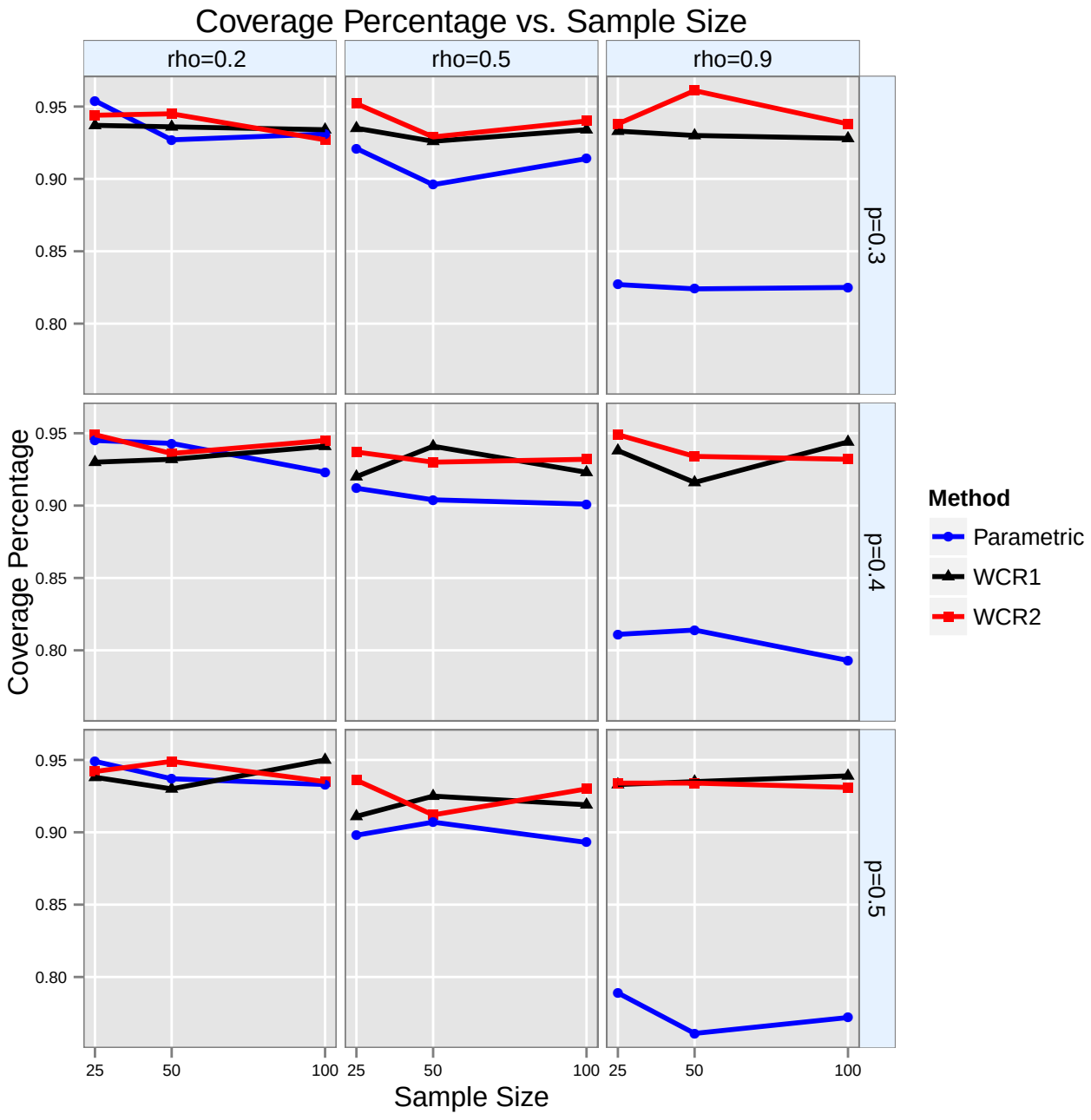

Figure 3.1: The coverage percentage of the 95% confidence intervals of traditional parametric method and the two proposed parametric WCR methods for normal clustered ROC data

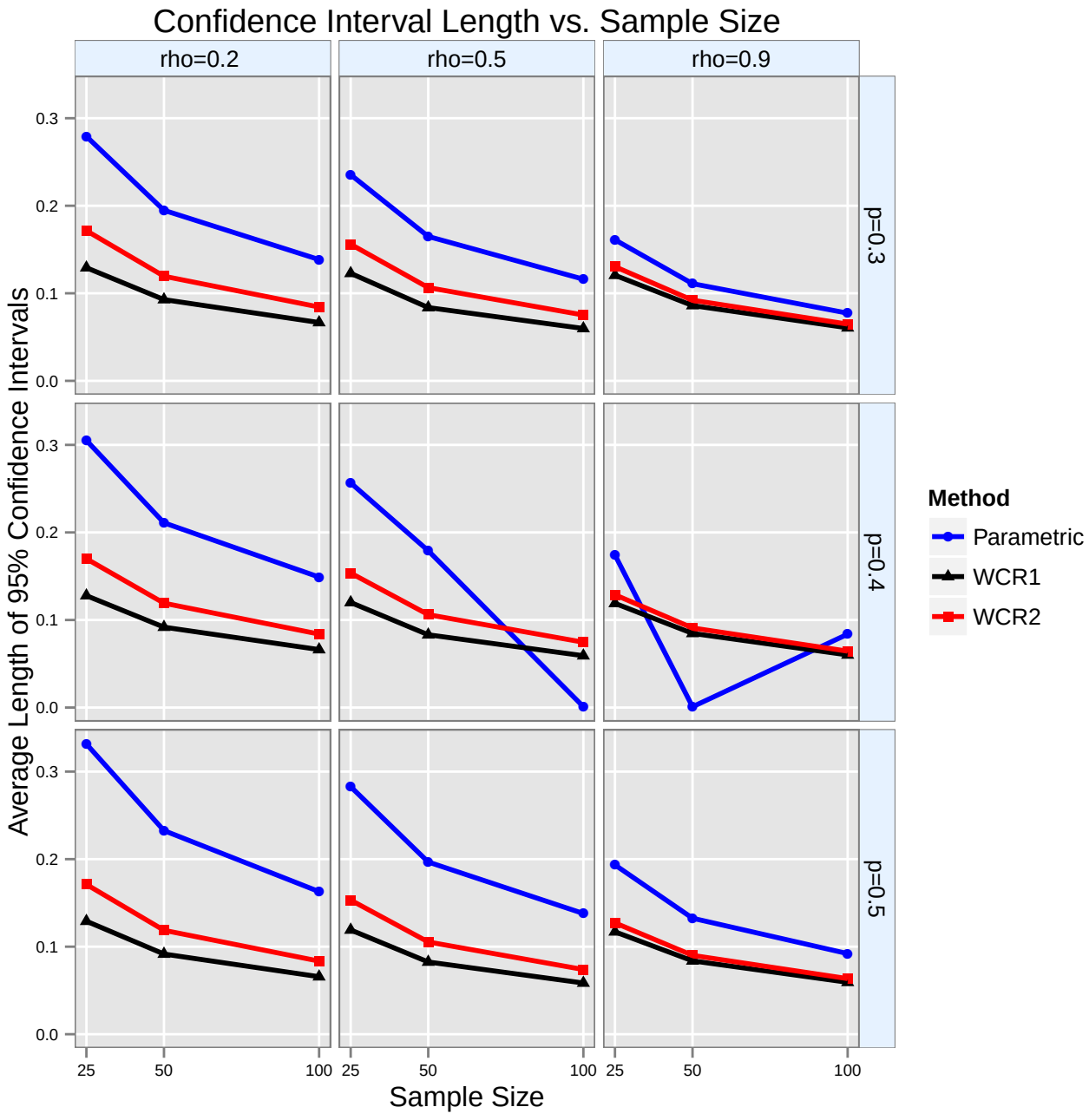

Figure 3.2: The average length of the 95% confidence intervals of traditional parametric method and the two proposed parametric WCR methods for normal clustered ROC data

Table 3.3: Simulation results for normal clustered ROC data using three nonparametric methods

			WCR1				Obuchowski				Nonparametric			
p	ρ	n	Bias (%)	RMSE	CP	Length	Bias (%)	RMSE	CP	Length	Bias (%)	RMSE	CP	Length
0.3	0.2	25	0.1850	0.0445	0.965	0.1847	-0.0234	0.0381	0.946	0.1591	0.1044	0.0416	0.935	0.1555
		50	0.0809	0.0305	0.950	0.1239	-0.0248	0.0269	0.948	0.1122	0.0441	0.0283	0.947	0.1091
		100	0.0163	0.0218	0.945	0.0867	0.0915	0.0191	0.951	0.0794	0.0204	0.0204	0.937	0.0769
	0.5	25	0.0456	0.0398	0.959	0.1685	0.1184	0.0332	0.953	0.1470	0.0708	0.0374	0.927	0.1333
		50	-0.0630	0.0283	0.953	0.1147	-0.0126	0.0236	0.949	0.1036	-0.0694	0.0267	0.921	0.0935
		100	0.0273	0.0203	0.944	0.0796	-0.0770	0.0166	0.952	0.0732	0.0095	0.0191	0.915	0.0660
	0.9	25	-0.0457	0.0353	0.956	0.1491	-0.3693	0.0274	0.933	0.1343	-0.2128	0.0348	0.805	0.0938
		50	0.1214	0.0238	0.958	0.1009	-0.0936	0.0187	0.954	0.0929	0.0177	0.0228	0.835	0.0650
		100	-0.0275	0.0161	0.952	0.0694	-0.1087	0.0133	0.949	0.0650	-0.0717	0.0160	0.860	0.0456
0.4	0.2	25	-0.1280	0.0435	0.971	0.1862	0.4147	0.0395	0.926	0.1591	-0.1879	0.0414	0.942	0.1556
		50	-0.0621	0.0312	0.947	0.1244	0.1907	0.0265	0.939	0.1127	-0.1291	0.0293	0.928	0.1091
		100	-0.0914	0.0210	0.953	0.0863	0.0617	0.0202	0.928	0.0794	-0.0691	0.0198	0.949	0.0769
	0.5	25	0.1354	0.0395	0.953	0.1687	0.0488	0.0341	0.929	0.1481	0.0455	0.0373	0.926	0.1333
		50	0.0372	0.0279	0.959	0.1147	0.0982	0.0237	0.951	0.1050	0.0413	0.0267	0.921	0.0937
		100	-0.0611	0.0198	0.949	0.0796	-0.0156	0.0169	0.945	0.0738	-0.0487	0.0185	0.927	0.0659
	0.9	25	-0.0526	0.0343	0.944	0.1495	-0.2709	0.0282	0.927	0.1379	-0.2111	0.0344	0.809	0.0942
		50	-0.0735	0.0230	0.952	0.1005	-0.0952	0.0194	0.954	0.0950	-0.0897	0.0228	0.849	0.0651
		100	0.0538	0.0166	0.952	0.0693	-0.0887	0.0139	0.940	0.0667	-0.0034	0.0170	0.827	0.0456
0.5	0.2	25	-0.1611	0.0439	0.960	0.1861	-0.1324	0.0376	0.938	0.1599	-0.1405	0.0409	0.942	0.1561
		50	0.0040	0.0294	0.945	0.1249	0.0603	0.0266	0.951	0.1136	0.0512	0.0277	0.952	0.1100
		100	-0.1000	0.0217	0.942	0.0871	0.0480	0.0181	0.956	0.0803	-0.0604	0.0201	0.944	0.0775
	0.5	25	0.2082	0.0393	0.959	0.1699	-0.1505	0.0343	0.920	0.1500	0.1161	0.0377	0.918	0.1344
		50	0.0174	0.0275	0.946	0.1152	0.0743	0.0248	0.941	0.1061	-0.0584	0.0259	0.924	0.0944
		100	-0.0336	0.0196	0.950	0.0802	0.0105	0.0168	0.939	0.0747	-0.0362	0.0191	0.921	0.0663
	0.9	25	0.1363	0.0350	0.953	0.1489	-0.2233	0.0278	0.948	0.1396	-0.0346	0.0358	0.804	0.0943
		50	0.1175	0.0239	0.952	0.1005	-0.0575	0.0195	0.947	0.0971	0.0442	0.0251	0.800	0.0655
		100	0.1205	0.0167	0.953	0.0693	-0.0791	0.0136	0.951	0.0681	0.0941	0.0177	0.808	0.0458

WCR-the proposed nonparametric WCR method;
Obuchowski-Obuchowski's nonparametric method for clustered ROC data;
Nonparametric-the nonparametric ROC method for independent ROC data;
RMSE-square root of mean squared error;
CP-coverage percentage of 95% confidence intervals;
Length- the average length of the 95% confidence intervals.

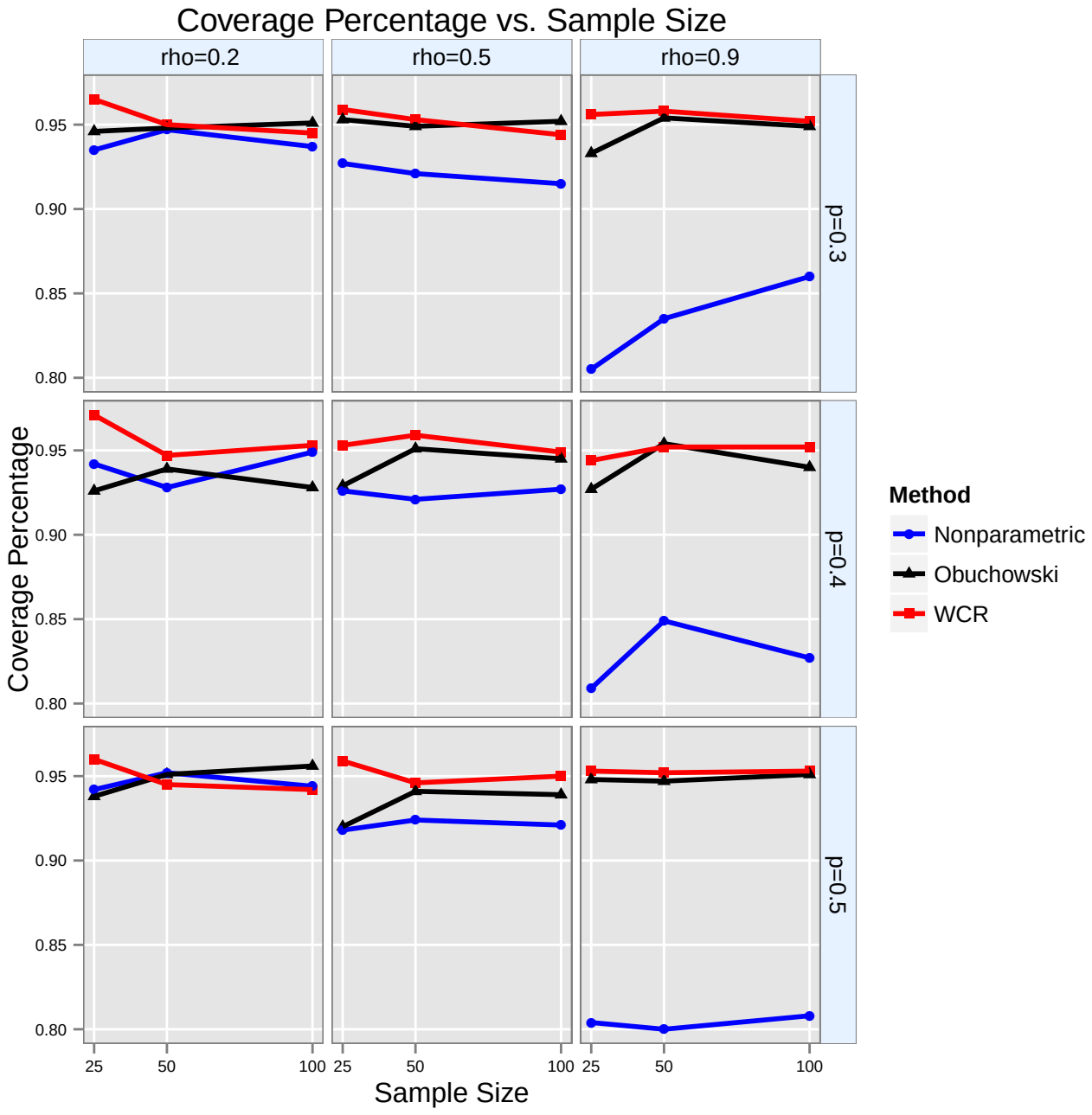

Figure 3.3: The coverage percentage of the 95% confidence intervals of traditional nonparametric method, Obuchowski's nonparametric method and proposed nonparametric WCR method for lognormal clustered ROC data

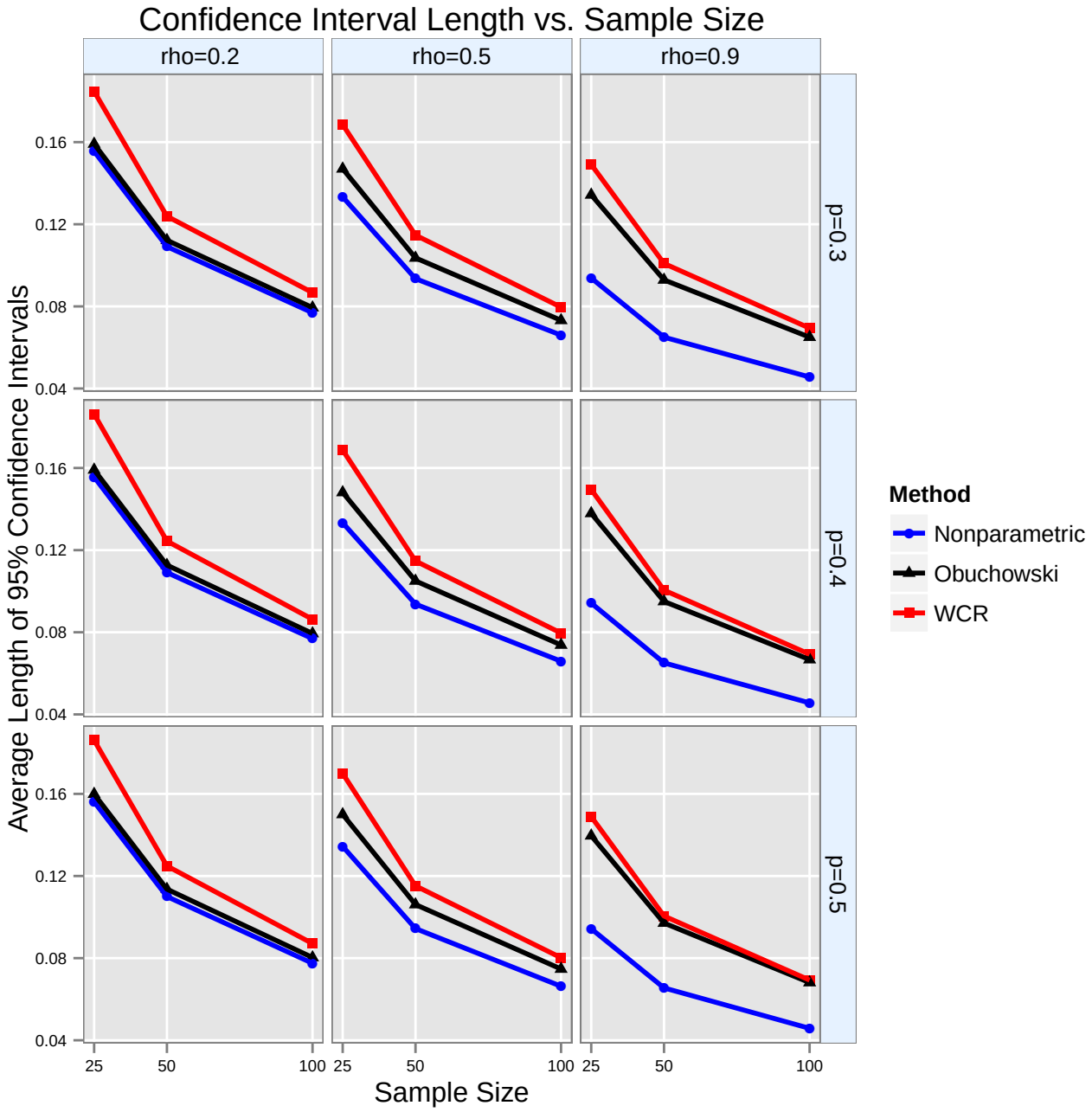

Figure 3.4: The average length of the 95% confidence intervals of nonparametric method, Obuchowski's nonparametric method and proposed nonparametric WCR methods for lognormal clustered ROC data

Table 3.4: Simulation results for lognormal clustered ROC data using three nonparametric methods

			WCR1				Obuchowski				Nonparametric			
p	ρ	n	Bias (%)	RMSE	CP	Length	Bias (%)	RMSE	CP	Length	Bias (%)	RMSE	CP	Length
0.3	0.2	25	0.0249	0.0436	0.972	0.1841	-0.0910	0.0368	0.953	0.1581	-0.0343	0.0411	0.950	0.1544
		50	0.0742	0.0307	0.956	0.1247	0.1141	0.0259	0.955	0.1122	0.0665	0.0288	0.937	0.1089
		100	0.0009	0.0221	0.936	0.0863	0.0335	0.0188	0.949	0.0791	-0.0195	0.0211	0.930	0.0768
	0.5	25	0.2235	0.0397	0.965	0.1695	0.1241	0.0339	0.945	0.1469	0.1921	0.0378	0.915	0.1334
		50	0.0088	0.0286	0.945	0.1144	0.0796	0.0231	0.959	0.1040	-0.0121	0.0271	0.908	0.0939
		100	-0.0645	0.0196	0.961	0.0798	-0.1292	0.0177	0.931	0.0733	-0.1108	0.0184	0.926	0.0660
	0.9	25	-0.1384	0.0346	0.962	0.1494	-0.3484	0.0267	0.937	0.1337	-0.3238	0.0338	0.826	0.0939
		50	-0.0593	0.0240	0.963	0.1001	-0.0050	0.0188	0.948	0.0925	-0.1547	0.0235	0.819	0.0649
		100	-0.0672	0.0165	0.965	0.0694	-0.1051	0.0136	0.939	0.0651	-0.1517	0.0165	0.821	0.0456
0.4	0.2	25	-0.1327	0.0424	0.972	0.1860	0.0036	0.0382	0.937	0.1603	-0.2158	0.0415	0.931	0.1554
		50	-0.0451	0.0320	0.938	0.1244	-0.0087	0.0261	0.962	0.1126	-0.0154	0.0298	0.924	0.1092
		100	0.0303	0.0217	0.956	0.0868	0.0515	0.0191	0.945	0.0796	0.0320	0.0202	0.943	0.0771
	0.5	25	-0.0769	0.0396	0.961	0.1685	-0.1375	0.0331	0.940	0.1479	-0.0817	0.0380	0.916	0.1334
		50	-0.0553	0.0285	0.936	0.1148	-0.1261	0.0236	0.948	0.1046	-0.0411	0.0270	0.910	0.0937
		100	0.0744	0.0194	0.951	0.0798	0.0279	0.0166	0.947	0.0741	0.0836	0.0186	0.918	0.0662
	0.9	25	0.2069	0.0349	0.958	0.1493	-0.1887	0.0277	0.942	0.1370	0.1186	0.0357	0.804	0.0937
		50	0.1123	0.0248	0.948	0.1008	-0.1598	0.0197	0.932	0.0956	0.0409	0.0249	0.801	0.0653
		100	-0.0407	0.0173	0.954	0.0691	-0.0013	0.0138	0.944	0.0667	-0.1026	0.0173	0.814	0.0456
0.5	0.2	25	-0.1236	0.0436	0.974	0.1874	0.0694	0.0390	0.926	0.1608	-0.1494	0.0410	0.936	0.1565
		50	0.1181	0.0300	0.961	0.1254	0.0599	0.0269	0.944	0.1135	0.1206	0.0288	0.946	0.1101
		100	0.1051	0.0218	0.949	0.0873	0.0006	0.0182	0.957	0.0803	0.1690	0.0199	0.955	0.0776
	0.5	25	-0.0092	0.0406	0.971	0.1699	-0.1033	0.0325	0.951	0.1496	-0.0042	0.0393	0.902	0.1343
		50	-0.0598	0.0275	0.961	0.1151	0.0823	0.0242	0.946	0.1059	-0.0509	0.0268	0.916	0.0944
		100	-0.1076	0.0193	0.958	0.0800	0.0480	0.0173	0.943	0.0749	-0.1055	0.0189	0.920	0.0664
	0.9	25	-0.1962	0.0336	0.952	0.1495	-0.2603	0.0283	0.936	0.1404	-0.2467	0.0353	0.805	0.0947
		50	-0.0655	0.0241	0.955	0.1007	-0.1511	0.0200	0.932	0.0973	-0.1697	0.0249	0.812	0.0656
		100	0.0425	0.0167	0.963	0.0692	-0.0741	0.0137	0.946	0.0680	0.0135	0.0174	0.811	0.0459

WCR-the proposed nonparametric WCR method;
Obuchowski-Obuchowski's nonparametric method for clustered ROC data;
Nonparametric-the nonparametric ROC method for independent ROC data;
RMSE-square root of mean squared error;
CP-coverage percentage of 95% confidence intervals;
Length- the average length of the 95% confidence intervals.

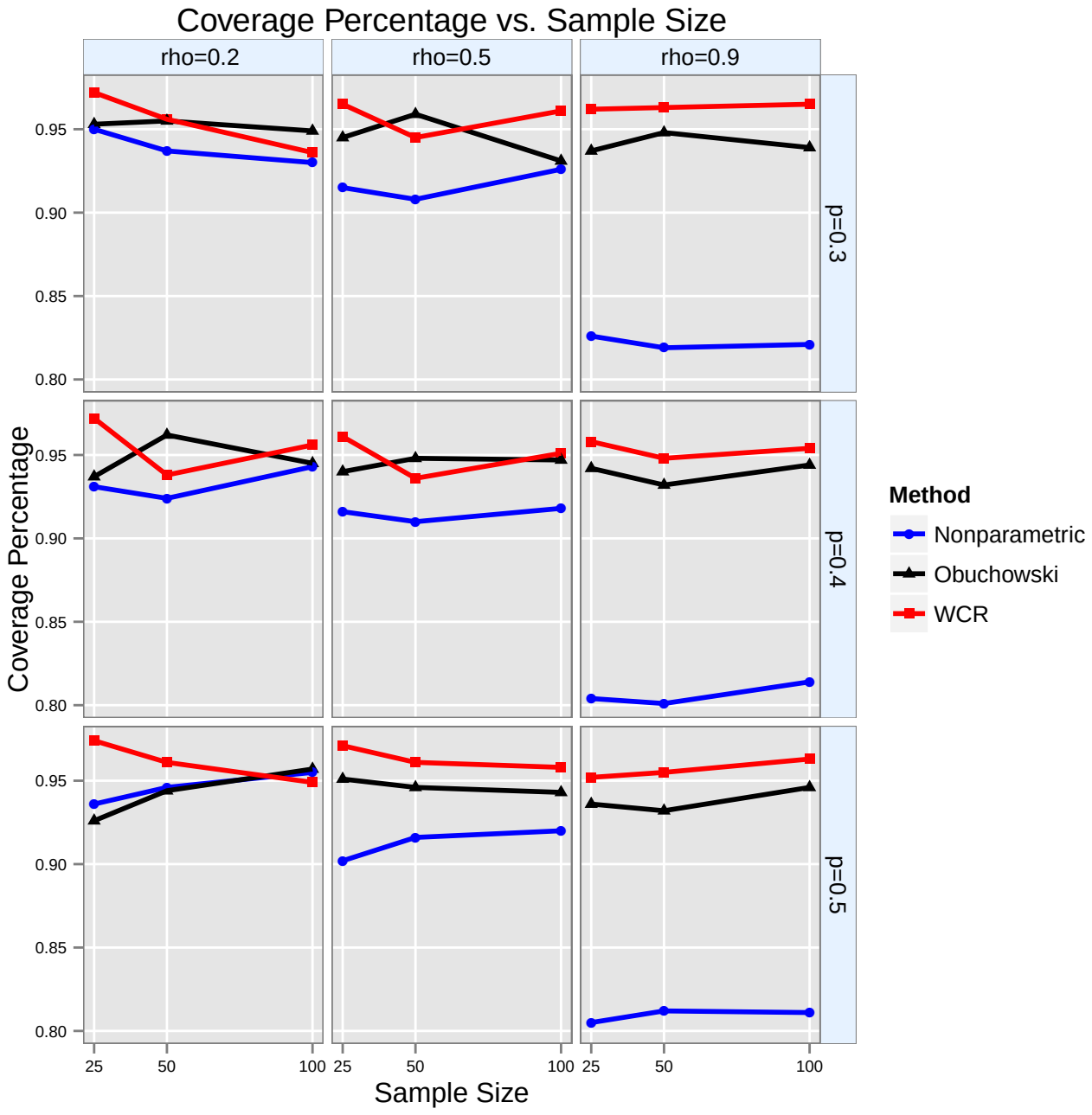

Figure 3.5: The coverage percentage of the 95% confidence intervals of traditional nonparametric method, Obuchowski's nonparametric method and proposed nonparametric WCR method for lognormal clustered ROC data

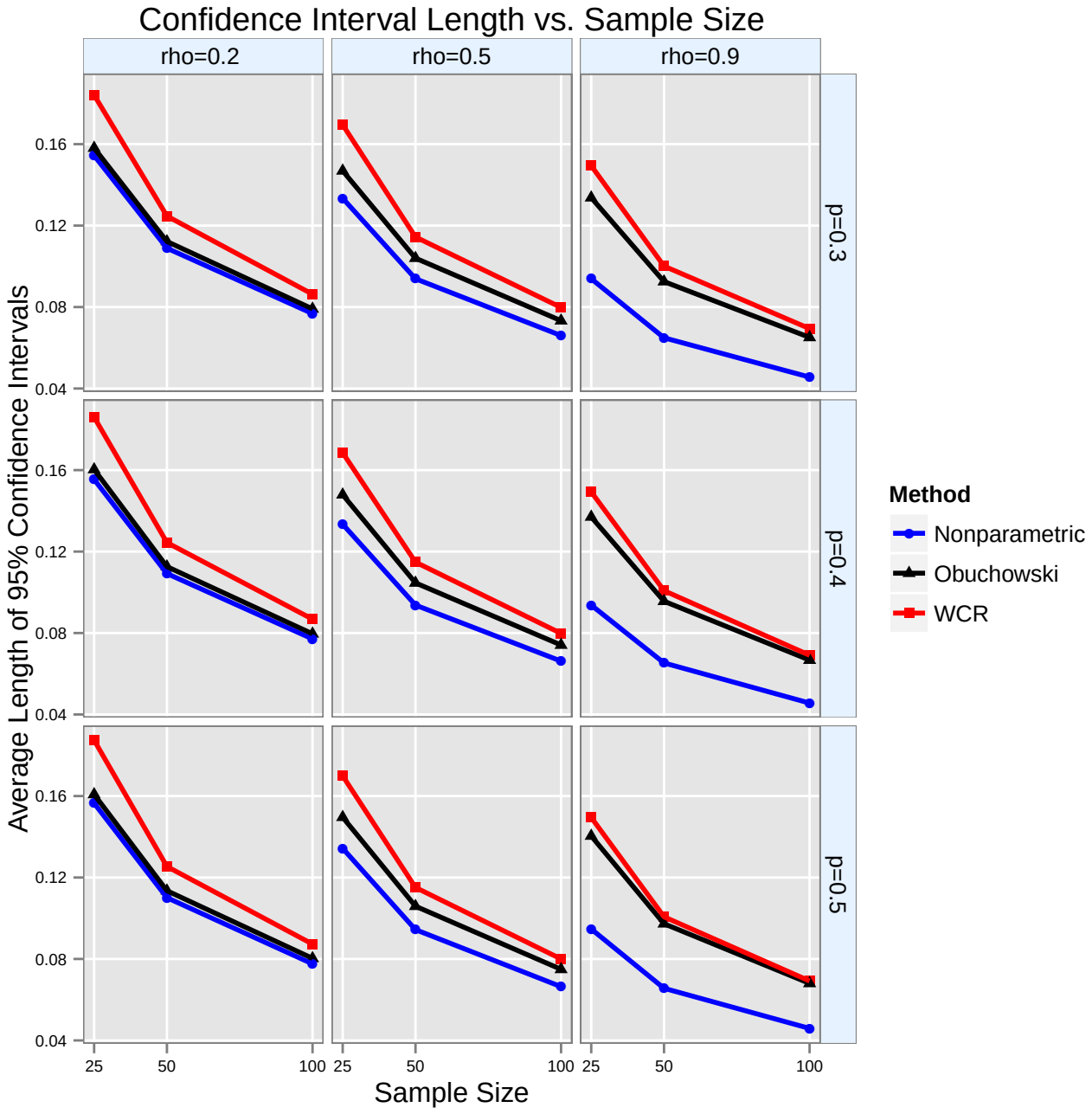

Figure 3.6: The average length of the 95% confidence intervals of nonparametric method, Obuchowski's nonparametric method and proposed nonparametric WCR methods for lognormal clustered ROC data

Chapter 4: WCR Methods for Covariate Adjusted ROC Curves

4.1 Estimating Covariate Adjusted ROC Curves

Let T_{ij} denote the jth continuous biomarker result in the ith cluster, where $i = 1, \ldots, I$, $j = 1, \ldots, n_i$. Each cluster might have either diseased results, or nondiseased results or both of them. Denote X as the vector of patient covariates. The location disease status is denoted as D, where $D = 1$ for a diseased location and $D = 0$ for a nondiseased location. Assume T follows distribution $F_{d,x}(c) = P(T < c|D = d, X = x)$ given $D = d$ and $X = x$ and let $S_{d,x}(c) = 1 - F_{d,x}(c)$ be the survival function of T.

For the qth resample, $q = 1, \ldots, Q$, we randomly select one biomarker result out of n_i from the ith cluster, and denote the selected observation $T^*_{i,q}$, which can either be from a diseased or a nondiseased location. The qth ROC curve and corresponding AUC can be estimated by the resampled data, $T^*_{i,q}, i = 1, \ldots, I$, using either indirect regression model or direct regression model to adjust for the covariate effects. We have $T^*_{i,q}$ follows distribution $\hat{F}_{d,x}(c)$ given $D = d$ and $X = x$ and its survival function is $\hat{S}_{d,x}(c)$. The qth ROC curve associated with covariate X, $\widehat{ROC}^*_{x,q}(u)$, is estimated by

$$\widehat{ROC}^*_{x,q}(u) = \hat{S}^*_{1,x}(\hat{S}^{-1*}_{0,x}(u)), \tag{4.1}$$

where $\hat{S}^{-1*}_{0,x}(u)$ is the inverse function of $\hat{S}^*_{0,x}(c)$. So the qth weighted AUC (wAUC) is estimated by

$$\widehat{wAUC}^*_{x,q}(u) = \int_0^1 \widehat{ROC}^*_{x,q}(u) dW(u). \tag{4.2}$$

The qth area under ROC curve is estimated by

$$\widehat{AUC}^*_{x,q} = \int_0^1 \widehat{ROC}^*_{x,q}(u)du. \tag{4.3}$$

The qth partial area under the curve between FPRs u_0 and u_1, which is estimated by

$$\widehat{pAUC}^*_{x,q}(u_0, u_1) = \frac{1}{u_1 - u_0} \int_{u_0}^{u_1} \widehat{ROC}^*_{x,q}(u)du. \tag{4.4}$$

To obtain the WCR wAUC and WCR AUC estimators, we can simply take the average on all the resampled wAUC or AUC estimators, that is,

$$\widehat{wAUC}_{WCR} = \frac{1}{Q} \sum_{q=1}^{Q} \widehat{wAUC}^*_q, \tag{4.5}$$

and

$$\widehat{AUC}_{WCR} = \frac{1}{Q} \sum_{q=1}^{Q} \widehat{AUC}^*_q. \tag{4.6}$$

In order to estimate the variance of the WCR ROC curve and the wAUC estimator, we fist estimate the variance of the qth ROC curve and the wAUC estimator using the bootstrap method. For the qth resampled data, each bootstrap sample is generated by sampling with replacement from the data, and a bootstrap ROC curve $\widehat{ROC}^*_{x,b,q}$ where $b = 1, \ldots, B$ as well as a bootstrap wAUC estimator $\widehat{AUC}^*_{x,b,q}$ could be estimated by the bootstrap data. If we bootstrap B times, we got B bootstrap ROC curves and bootstrap wAUC estimators. The bootstrap variance of the qth ROC curve and variance of the qth wAUC estimator are estimated by

$$\widehat{var}(ROC^*_q) = \frac{1}{B-1} \sum_{b=1}^{B} (\widehat{ROC}^*_{x,b,q} - \widehat{ROC}^*_{x,q}). \tag{4.7}$$

$$\widehat{var}(wAUC_q^*) = \frac{1}{B-1}\sum_{b=1}^{B}(\widehat{wAUC}_{x,b,q}^* - \widehat{wAUC}_{x,q}^*). \tag{4.8}$$

Thus, we could apply the WCR method to get the variance of the WCR ROC curve and the variance of the WCR wAUC estimator by

$$\widehat{var}(\widehat{ROC}_{WCR}) = \frac{1}{Q}\sum_{q=1}^{Q}\widehat{var}(\widehat{ROC}_q^*) - S_{ROC}^2, \tag{4.9}$$

and

$$\widehat{var}(\widehat{wAUC}_{WCR}) = \frac{1}{Q}\sum_{q=1}^{Q}\widehat{var}(\widehat{AUC}_q^*) - S_{AUC}^2, \tag{4.10}$$

where

$$S_{ROC}^2 = \frac{1}{Q-1}\sum_{q=1}^{Q}(\widehat{ROC}_q^* - \widehat{ROC}_{WCR})^2, \tag{4.11}$$

and

$$S_{wAUC}^2 = \frac{1}{Q-1}\sum_{q=1}^{Q}(\widehat{wAUC}_q^* - \widehat{wAUC}_{WCR})^2. \tag{4.12}$$

4.1.1 WCR Indirect Regression Methods

Firstly, we propose WCR indirect regression methods for clustered ROC data with covariates. For the qth resample, $q = 1, \ldots, Q$, we randomly select one biomarker result from the ith cluster, and denote the selected observation as $T_{i,q}^*, i = 1, \ldots, I$, which can be expressed in the following linear regression model

$$T_q^* = \hat{\mu}(D, X; \hat{\beta}_q^*) + \hat{\sigma}(D, X; \hat{\alpha}_q^*)\hat{\epsilon}, \tag{4.13}$$

where X denotes the covariates, D denotes the disease status and the residual ϵ has mean 0 and variance 1 with an unknown survival function S_ϵ. Hence, for covariate $X = x$ and $D = d$, the qth

ROC curve is given by

$$\widehat{ROC}^*_{x,q}(u) = \hat{S}^*_\epsilon(\hat{b}^*_q(x;\hat{\alpha}^*_q)\hat{S}^{-1*}_\epsilon(u) - a^*_q(x;\hat{\beta}^*_q,\hat{\alpha}^*_q)), \tag{4.14}$$

where $\hat{S}^{-1*}_\epsilon(.)$ is the inverse function of $\hat{S}^*_\epsilon(.)$, $\hat{a}^*_q(x;\hat{\beta}^*_q,\hat{\alpha}^*_q) = (\hat{\mu}(d,x;\hat{\beta}^*_q) - \hat{\mu}(d,x;\hat{\beta}^*_q))/(\hat{\sigma}(d,x;\hat{\alpha}^*_q))$, and $\hat{b}^*_q(x;\hat{\alpha}^*_q) = \hat{\sigma}(d,x;\hat{\alpha}^*_q)/\hat{\sigma}(d,x;\hat{\alpha}^*_q)$.

The corresponding AUC could be estimated by integrating on $\widehat{ROC}^*_{x,q}(u)$ between 0 and 1.

$$\widehat{AUC}^*_{x,q} = \int_0^1 \widehat{ROC}^*_{x,q}(u)du. \tag{4.15}$$

Assume S_ϵ is the standard normal distribution, the qth AUC is estimated by,

$$\widehat{AUC}^*_{x,q} = \Phi(\frac{a^*_q(x;\hat{\beta}^*_q,\hat{\alpha}^*_q)}{\sqrt{1+(b^*_q(x;\hat{\alpha}^*_q))^2}}). \tag{4.16}$$

To obtain the WCR ROC curve, we can first average all the resampled parameters,

$$\hat{a}_{WCR}(x) = \frac{1}{Q}\sum_{q=1}^{Q}\hat{a}^*_q(x;\hat{\beta}^*_q,\hat{\alpha}^*_q), \tag{4.17}$$

and

$$\hat{b}_{WCR}(x) = \frac{1}{Q}\sum_{q=1}^{Q}\hat{b}^*_q(x;\hat{\alpha}^*_q). \tag{4.18}$$

The WCR ROC curve is estimated by

$$\widehat{ROC}_{x,WCR}(u) = \hat{S}_\epsilon(\hat{b}_{WCR}(x)\hat{S}^{-1}_\epsilon(u) - a_{WCR}(x)), \tag{4.19}$$

The corresponding WCR AUC could be estimated by taking integral on $\widehat{ROC}_{x,WCR}(u)$ between 0 and 1,

$$\widehat{AUC}_{x,WCR} = \int_0^1 \widehat{ROC}_{x,WCR}(u)du. \tag{4.20}$$

For the case where S_ϵ is the standard normal distribution, we can estimate WCR AUC by plugging in WCR parameters,

$$\widehat{AUC}_{x,WCR} = \Phi(\frac{\hat{a}_{WCR}(x)}{\sqrt{1+(\hat{b}_{WCR}(x))^2}}). \tag{4.21}$$

Another way to estimate WCR ROC curve and corresponding AUC is to take the average on all the resampled $\widehat{ROC}^*_{x,q}$ and $\widehat{AUC}^*_{x,q}$

$$\widehat{ROC}_{x,WCR} = \frac{1}{Q}\sum_{q=1}^{Q}\widehat{ROC}^*_{x,q}, \tag{4.22}$$

and

$$\widehat{AUC}_{x,WCR} = \frac{1}{Q}\sum_{q=1}^{Q}\widehat{AUC}^*_{x,q}. \tag{4.23}$$

Consider a simple example with $X = x_1$ and $D = d$ to illustrate how the WCR method works on estimating the parameters and the ROC curve. For the qth resampled data $T*_q$, we have $\mu(d, x_1; \beta^*_q) = \beta^*_{0,q} + \beta^*_{1,q}d + \beta^*_{2,q}x_1 + \beta^*_{3,q}(d * x_1)$. The variance $\sigma^{2*}_q(d, x; \alpha)$ does not depend on covariates, therefore it can be written as $\sigma^2(d, x_1; \alpha^*_q) = \sigma^{2*}_q(d)$. The parameters $a(x; \beta, \alpha)$ and $b(x; \alpha)$ are given by $a^*_q(x_1; \beta^*_q) = (\beta^*_{1,q} + \beta^*_{3,q}x_1)/\sigma(1)$ and $b^*_q(x_1; \alpha^*_q) = \sigma(0)/\sigma(1)$. The qth ROC curve associated with covariates $X = x_1$ is estimated by

$$\widehat{ROC}^*_{x_1,q}(u) = \hat{S}_\epsilon(\frac{\hat{\sigma}(0)}{\hat{\sigma}(1)}\hat{S}^{-1}_\epsilon(u) - \frac{\hat{\beta}^*_{1,q} + \hat{\beta}^*_{3,q}x_1}{\hat{\sigma}(1)}). \tag{4.24}$$

The corresponding AUC is estimated by integrating on $\widehat{ROC}^*_{x_1,q}(u)$ between 0 and 1.

$$\widehat{AUC}^*_{x_1,q} = \int_0^1 \widehat{ROC}^*_{x,q}(u)du. \tag{4.25}$$

To estimate the WCR ROC curve, we can obtain the WCR parameters $\hat{\beta}_{1,WCR}$,$\hat{\beta}_{3,WCR}$ by averaging all the resampled estimators ($\hat{\beta}^*_{1,q}$,$\hat{\beta}^*_{3,q}$), that is

$$\hat{\beta}_{1,WCR} = \frac{1}{Q}\sum_{q=1}^{Q}\hat{\beta}^*_{1,q}. \tag{4.26}$$

and

$$\hat{\beta}_{3,WCR} = \frac{1}{Q}\sum_{q=1}^{Q}\hat{\beta}^*_{3,q}. \tag{4.27}$$

So the WCR ROC curve is estimated by

$$\widehat{ROC}_{x_1,WCR}(u) = \hat{S}_\epsilon(\frac{\hat{\sigma}(0)}{\hat{\sigma}(1)}\hat{S}_\epsilon^{-1}(u) - \frac{\hat{\beta}_{1,WCR} + \hat{\beta}_{3,WCR}x_1}{\hat{\sigma}(1)}). \tag{4.28}$$

The WCR wAUC and WCR AUC are estimated by integrating on $\widehat{ROC}^*_{x_1,WCR}(u)$ between 0 and 1, that is

$$\widehat{wAUC}_{x_1,WCR} = \int_0^1 \widehat{ROC}_{x_1,WCR}(u)dW(u), \tag{4.29}$$

and

$$\widehat{AUC}_{x_1,WCR} = \int_0^1 \widehat{ROC}_{x_1,WCR}(u)du. \tag{4.30}$$

The WCR AUC could also be estimated by averaging all the resampled $\widehat{AUC}^*_{x,q}$,

$$\widehat{AUC}_{x_1,WCR} = \frac{1}{Q}\sum_{q=1}^{Q}\widehat{AUC}^*_{x_1,q}. \tag{4.31}$$

4.1.2 WCR Direct Regression Methods

We propose within-cluster resampling direct regression method in this section. For the qth resampled data $T^*_{i,q}$, $q = 1,\ldots,Q$, we rearrange the data so that the first d_q selected observations are diseased biomarker results, denoted as $T^*_{i_1,q}$, $i_1 = 1\ldots d_q$, and the rest of the selected observations are nondiseased biomarker results, denoted as $T^*_{i_2,q}$, $i_2 = d_q + 1\ldots I$.

The qth ROC curve associated with covariates $X = x$ is,

$$ROC^*_{x,q}(u) = g\{H(u) + \beta^*_q x\}, \tag{4.32}$$

where $g(.)$ is the link function, $H(u)$ is a baseline monotone increasing function of, and $\beta^*_q \boldsymbol{X}$ is a linear regression model which summarizes the effect of the patient covariates $\boldsymbol{X}$. For binormal model, we have

$$ROC^*_{x,q}(u) = \Phi\{\alpha^*_{0,q} + \alpha^*_{1,q}\Phi^{-1}(u) + \beta^*_q x\}, \tag{4.33}$$

To estimate the WCR ROC estimators, we could first estimate the qth ROC estimators by the generalized linear model method. The qth indicator variable $U^*_{i_1 i_2,q} = I[T^*_{i_1,q} \geq T^*_{i_2,q}]$ contains all the possible pairs of the qth resampled biomarker results. The qth parameters β^*_q are estimated by solving the estimating equation

$$\sum_{i_1=1}^{d_q}\sum_{i_2=1}^{I}\frac{U^*_{i_1 i_2,q} - g\{\beta^*_q x + h(u_{i_2})\}}{g\{\beta^*_q x + h(u_{i_2})\}(1 - g\{\beta^*_q x + h(u_{i_2})\})}\frac{\partial g\{\beta^*_q x + h(u_{i_2})\}}{\partial \beta^*_q} = 0. \tag{4.34}$$

The qth ROC curve then is

$$\widehat{ROC}^*_{x,q}(u) = g\{H(u) + \hat{\beta}^*_q x\}. \tag{4.35}$$

The qth wAUC is estimated by

$$\widehat{wAUC}^*_{x,q} = \int_0^1 \widehat{ROC}^*_{x,q}(u) dW(u). \tag{4.36}$$

If we choose the weight $W = 1$, the qth AUC is estimated by

$$\widehat{AUC}^*_{x,q} = \int_0^1 \widehat{ROC}^*_{x,q}(u) du. \tag{4.37}$$

To estimate the WCR ROC estimators. We can simply average all the resampled ROC parameter estimators. We have

$$\hat{\beta}_{WCR} = \frac{1}{Q} \sum_{q=1}^{Q} \hat{\beta}^*_q. \tag{4.38}$$

So the WCR ROC curve associated with covariates $X = x$ is estimated by plugging in the WCR parameter estimators, that is,

$$\widehat{ROC}_{x,WCR}(u) = g\{H(u) + \hat{\beta}_{WCR} x\}, \tag{4.39}$$

and the WCR wAUC and AUC estimators are

$$\widehat{wAUC}_{x,WCR} = \int_0^1 \widehat{ROC}_{x,WCR}(u) dW(u), \tag{4.40}$$

and

$$\widehat{AUC}_{x,WCR} = \int_0^1 \widehat{ROC}_{x,WCR}(u) du. \tag{4.41}$$

The second way to estimate WCR ROC curves, WCR wAUC and AUC estimators associated with covariates $X = x$ is to average all the resampled ROC curves and resampled wAUCs and AUC estimators, that is,

$$\widehat{wAUC}_{x,WCR} = \frac{1}{Q}\sum_{q=1}^{Q}\widehat{wAUC}_q^*, \tag{4.42}$$

and

$$\widehat{AUC}_{x,WCR} = \frac{1}{Q}\sum_{q=1}^{Q}\widehat{AUC}_q^*. \tag{4.43}$$

In order to estimate the AUC estimator using qth resampled data, we could also fit a direct model using AUC regression method (Dodd 2001). The model is similar to ROC regression model,

$$g(AUC_q^*) = \beta_q^* x, \tag{4.44}$$

which is a generalized linear regression model for the binary variables $U_{i_1 i_2,q}^*$. Thus, to estimate the model parameters, we could solve the estimating function

$$\sum_{i_1=1}^{d_q}\sum_{i_2=1}^{I}\frac{U_{i_1 i_2,q}^* - g^{-1}\{\beta_q^* x\}}{g^{-1}\{\beta_q^* x\}(1-g^{-1}\{\beta_q^* x\})}\frac{\partial g^{-1}\{\beta_q^* x\}}{\partial \beta_q^*} = 0. \tag{4.45}$$

Two natural link functions are logit and probit. For a binary covariate, the logit link function could be used and the model is

$$logit(AUC_q^*) = \beta_{0,q}^* + \beta_{1,q}^* x. \tag{4.46}$$

For a continuous covariate, the probit link function is used and the model becomes

$$AUC_q^* = \Phi\{\beta_{0,q}^* + \beta_{1,q}^* x\}. \tag{4.47}$$

To create the indicator variable $U^*_{i_1 i_2,q}$, all the possible pairs $T^*_{i_1,q}$ and $T^*_{i_2,q}$ are created. The nature of the covariates need to be considered for pairing. For ordinal or categorical covariates, assume there are sufficient observations at each covariate level, the pairs are created with in each covariate level. For continuous data, pairs are created for all diseased and nondiseased observations and a difference of covariates term should be added in the model. For the qth resampled data, denote the covariates for the diseased and nondiseased biomarker results as $X_{i_1,D}$ and $X_{i_2,\bar{D}}$. The qth resample ROC curve associated with continuous covariates $X_D = x_D$ and $X_{\bar{D}} = x_{\bar{D}}$ is estimated by

$$ROC^*_{x_D,x_{\bar{D}},q}(u) = g\{H(u) + \beta^*_{q,1}x_D + \beta^*_{q,2}(x_D - x_{\bar{D}})\}. \tag{4.48}$$

Another way to accommodate for the continuous covariates is to pair all the observations with covariate values within a pre-specified range, which is denoted as

$$\mid X_{i_1,D} - X_{i_2,\bar{D}} \mid \leqslant \delta. \tag{4.49}$$

Thus the number of pairs depends on the choice of δ. For $\delta = 0$. the pairing is only created with the same covariate value. For $\delta = \infty$, we have all the pairs to estimate the ROC curve.

4.2 Simulation Study

In this section, we report the simulation studies to evaluate the performance of the proposed WCR indirect regression methods and WCR direct regression methods. We perform our methods on the simulated clustered ROC data to estimate the WCR parameters, AUC estimators and the corresponding WCR variance. We compare our methods with the traditional indirect regression method and show the bias in using the traditional method on clustered ROC data. We consider the situation where, for a diseased subject, there are either 2 or 5 diseased results plus 1 nondiseased result, for a nondiseased subject, all biomarker results in the same cluster are nondiseased.

Let I_1 and I_0 denote the number of clusters in the diseased group and the nondiseased group. We

let the two groups have the same number of clusters, so that $I_1 = I_0 = I/2$. The clusters in the diseased group have a cluster size $m_i = 3$ with probability p and a cluster size $m_i = 6$ with probability $1 - p$, where as the clusters in the nondiseased group have a cluster size $n_j = 2$ with probability $1 - p$ and a cluster size $n_j = 5$ with probability p. For a simplified ROC regression model, we simulate clustered ROC data such that , for the diseased group, $T \sim N(\boldsymbol{\mu}_X, \boldsymbol{\Sigma}_1)$, where $\boldsymbol{\mu}_X = (\mu_{D,X}, \mu_{D,X}, \mu_{\bar{D},X})$ when $m_i = 3$ and $\boldsymbol{\mu}_X = (\mu_{D,X}, \mu_{D,X}, \mu_{D,X}, \mu_{D,X}, \mu_{D,X}, \mu_{\bar{D},X})$ when $m_i = 6$. For the nondiseased group, $T \sim N(\boldsymbol{\mu}_{\bar{D},X}, \boldsymbol{\Sigma}_2)$, where $\boldsymbol{\mu}_{\bar{D},X} = (\mu_{D,X}, \mu_{\bar{D},X}, \mu_{D,X}, \mu_{\bar{D},X})$ when $n_j = 2$ and $\boldsymbol{\mu}_Y = (\mu_{\bar{D},X}, \mu_{\bar{D},X}, \mu_{\bar{D},X}, \mu_{\bar{D},X}, \mu_{\bar{D},X})$ when $n_j = 5$. The variance-covariance matrix $\boldsymbol{\Sigma}_1$ is a $m_i \times m_i$ matrix with first $m_i - 1$ diagonal elements equal to σ_1, the last one diagonal elements equal to σ_0 and correlation coefficients equal to ρ and $\boldsymbol{\Sigma}_2$ is a $n_j \times n_j$ matrix with diagonal elements equal to σ_0 and correlation coefficients equal to ρ.

We consider the informative cluster size correlation p of 0.3, 0.4 and 0.5. Note that when $p \neq 0.5$, the cluster size is different between the two groups. Under each setting, we consider the within-cluster correlation ρ of 0.2, 0.5, 0.9 and number of clusters in each group $I/2$ of 25, 50 and 100. For equal variance scenario, we consider $\sigma_1 = \sigma_0 = 1$. For unequal variance scenario, we consider $\sigma_1 = 2$ and $\sigma_0 = 1$.

4.2.1 Simulation Study for WCR Indirect Regression Methods

For the simulated clustered ROC data associated with covariate x_1, we employ the proposed WCR indirect methods as well as the traditional indirect regression method. We assume a simple regression model with covariate $X = x_1$, so that $\mu_{D,x_1} = \beta_0 + \beta_1 + \beta_2 x_1 + \beta_3 x_1$ and $\mu_{\bar{D},x_1} = \beta_0 + \beta_2 x_1$. To simplify the model, we let $\beta_0 = \beta_1 = \beta_2 = 0$ and $\beta_3 = 0.3$. Thus the ROC curve associated with covariate $X = x_1$ is

$$ROC_{x_1}(u) = S_\epsilon(\frac{\sigma(0)}{\sigma(1)} S_\epsilon^{-1}(u) - \frac{\beta_3 x_1}{\sigma(1)}). \tag{4.50}$$

We generate random variable x_1 following Uniform (0,10). to estimate the ROC curve model

parameter $\hat{\beta}_3$ and $\hat{\beta}_3/\hat{\sigma}_1$, we fit a simple regression model using least square method iF the diseased and nondiseased groups have equal variance. We fit a simple regression model using weighted least square iF the diseased and nondiseased groups have unequal variances. We let $x_1 = 2, 5, 9$ to estimate the AUCs, $\widehat{AUC}_{x_1=2}$, $\widehat{AUC}_{x_1=5}$ and $\widehat{AUC}_{x_1=9}$. The variance of the parameter estimator $\hat{\beta}_3$, $\hat{var}(\hat{\beta}_3)$, is estimated by the least square method or the weighted least square method. The variances of other estimators $\widehat{var}(\hat{\beta}_3/\hat{\sigma}_1)$ $\widehat{var}(\widehat{AUC})_{x_1=2}$, $\widehat{var}(\widehat{AUC})_{x_1=5}$ and $\widehat{var}(\widehat{AUC})_{x_1=9}$ are estimated by the bootstrap method. We obtain the parameter estimators $\hat{\beta}_3$ and $\hat{\beta}_3/\hat{\sigma}_1$, the AUC estimators, $\widehat{AUC}_{x_1=2}$, $\widehat{AUC}_{x_1=5}$ and $\widehat{AUC}_{x_1=9}$, and the corresponding 95% confidence intervals from both methods.

Tables 4.1, 4.3, 4.5, 4.7, 4.9 show the simulation results to compare the proposed WCR indirect method with traditional indirect method using β_3, β_3/σ_1, $AUC_{x_1=2}$, $AUC_{x_1=5}$ and $AUC_{x_1=9}$ under equal variance scenario. It is clear that the coverage percentages obtained by our methods are close to the nominal level and do not change as the within-cluster correlation becomes larger. Also the biases obtained by the proposed methods are very small. This indicates that proposed WCR method has a good performance on clustered ROC data associated with covariate X and can account for the within-cluster correlation. On the contrary, the coverage percentages obtained by the traditional indirect methods are not close to 95% and as within-cluster correlation increases, the coverage percentages decreases. Our method handles the within-cluster correlation better than the traditional methods do.

Tables 4.2, 4.4, 4.6, 4.8, 4.10 show the simulation results to compare the proposed WCR indirect method with the traditional indirect method using β_3, β_3/σ_1, $AUC_{x_1=2}$, $AUC_{x_1=5}$ and $AUC_{x_1=9}$ under unequal variance scenario. The same conclusions could be conduct as the conclusions under the equal variance scenario.

In Tables 4.1 and 4.2, we also compare the average length of the 95% confidence intervals of model coefficient β_3 from WCR indirect method and traditional indirect method. The proposed indirect method generate a larger length. As the within cluster correlation increases, the lengths of both methods increase. As the sample size increases, both lengths decrease.

We also visualize the simulation results through Figures 4.1, 4.2, 4.3, 4.2.

Table 4.1: Simulation results for β_3 using two indirect methods under equal variance setting

			WCR				Indirect			
p	rho	n	Bias (%)	RMSE	CP	Length	Bias (%)	RMSE	CP	Length
0.3	0.2	25	-0.2404	0.0702	0.920	1.6456	0.1454	0.0659	0.891	1.3396
		50	-0.1515	0.0475	0.948	1.1309	0.1547	0.0442	0.917	0.9305
		100	0.0879	0.0328	0.957	0.7972	0.0624	0.0312	0.916	0.6540
	0.5	25	0.2470	0.0788	0.935	1.3396	0.1250	0.0755	0.851	1.3280
		50	0.0982	0.0563	0.947	1.3100	0.0062	0.0542	0.821	0.9274
		100	0.0525	0.0375	0.952	0.9152	0.0476	0.0361	0.864	0.6513
	0.9	25	0.1614	0.0927	0.935	2.1783	0.0965	0.0890	0.772	1.3180
		50	0.2149	0.0645	0.940	1.5129	0.2513	0.0636	0.767	0.9230
		100	0.0931	0.0430	0.955	1.0556	0.0773	0.0417	0.795	0.6507
0.4	0.2	25	-0.1301	0.0678	0.935	1.6421	0.0348	0.0648	0.919	1.3498
		50	0.0398	0.0486	0.935	1.1302	0.1118	0.0461	0.907	0.9323
		100	-0.0788	0.0328	0.944	0.7870	0.0232	0.0312	0.923	0.6548
	0.5	25	0.2759	0.0783	0.950	1.8754	0.1438	0.0780	0.842	1.3297
		50	-0.0987	0.0527	0.950	1.2929	-0.1000	0.0525	0.852	0.9285
		100	0.1546	0.0365	0.959	0.9124	0.1391	0.0366	0.847	0.6552
	0.9	25	-0.1663	0.0907	0.937	2.1735	0.0761	0.0914	0.771	1.3181
		50	-0.2391	0.0632	0.950	1.4953	-0.1134	0.0646	0.759	0.9215
		100	0.0971	0.0449	0.935	1.0394	0.1438	0.0449	0.776	0.6505
0.5	0.2	25	-0.0909	0.0708	0.924	1.6481	0.0261	0.0676	0.897	1.3562
		50	0.0059	0.0481	0.934	1.1319	0.0249	0.0469	0.903	0.9400
		100	-0.2086	0.0345	0.947	0.7957	-0.1481	0.0337	0.886	0.6595
	0.5	25	0.2279	0.0782	0.928	1.8516	0.1381	0.0800	0.834	1.3343
		50	0.0359	0.0517	0.954	1.2800	0.1179	0.0539	0.864	0.9332
		100	0.2183	0.0374	0.949	0.9020	0.2480	0.0384	0.835	0.6577
	0.9	25	-0.2938	0.0898	0.946	2.1219	0.3172	0.0930	0.750	1.3163
		50	0.1373	0.0601	0.949	1.4750	0.1171	0.0645	0.757	0.9288
		100	-0.3579	0.0425	0.952	1.0336	-0.3061	0.0449	0.765	0.6570

WCR-the proposed WCR indirect method;
Indirect-the indirect ROC method;
RMSE-square root of mean squared error;
CP-coverage percentage of 95% confidence intervals;
Length- the average of simulated confidence interval lengths.

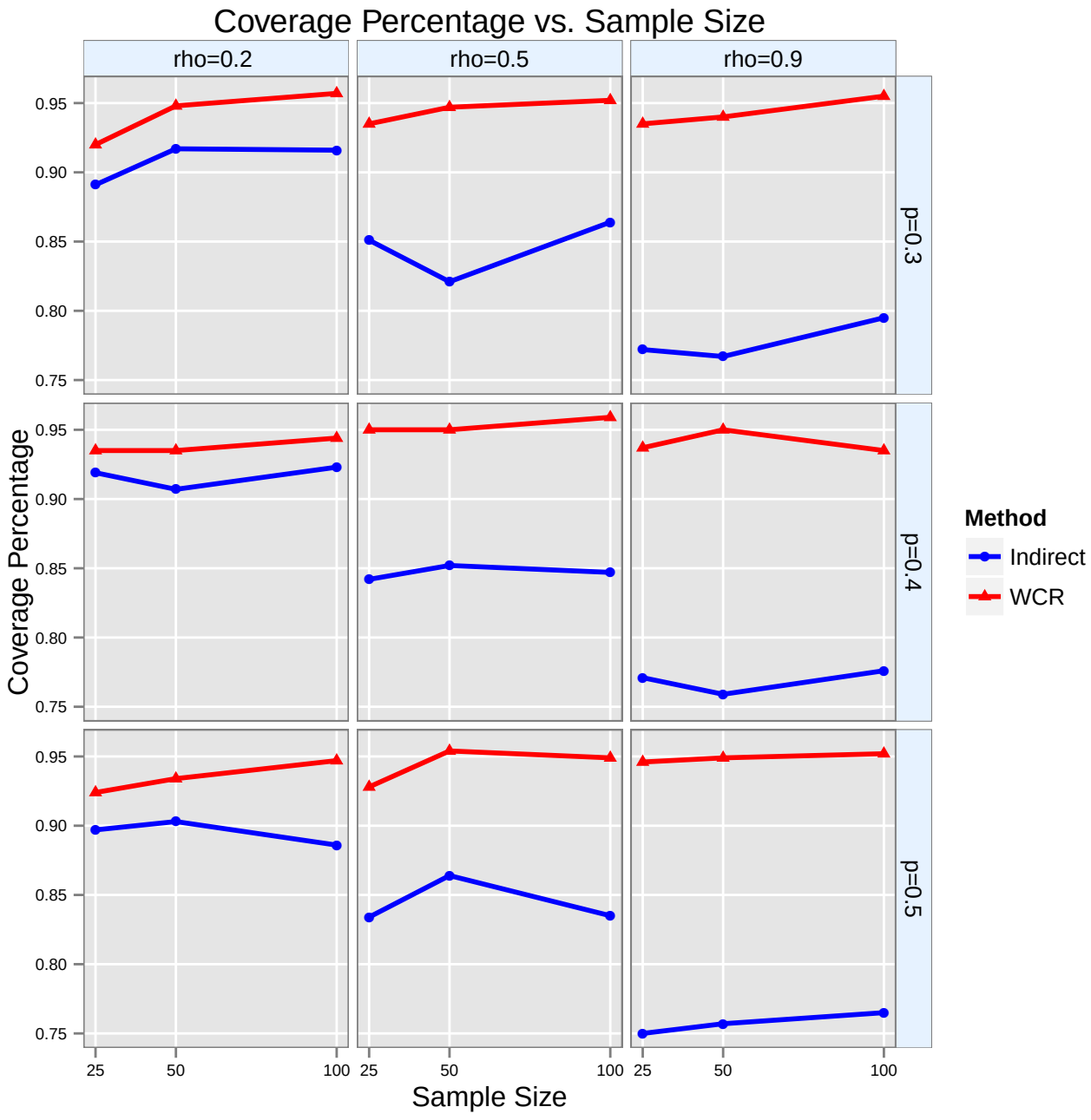

Figure 4.1: The coverage percentage of the 95% confidence intervals of indirect regression method and the proposed WCR indirect method under different settings

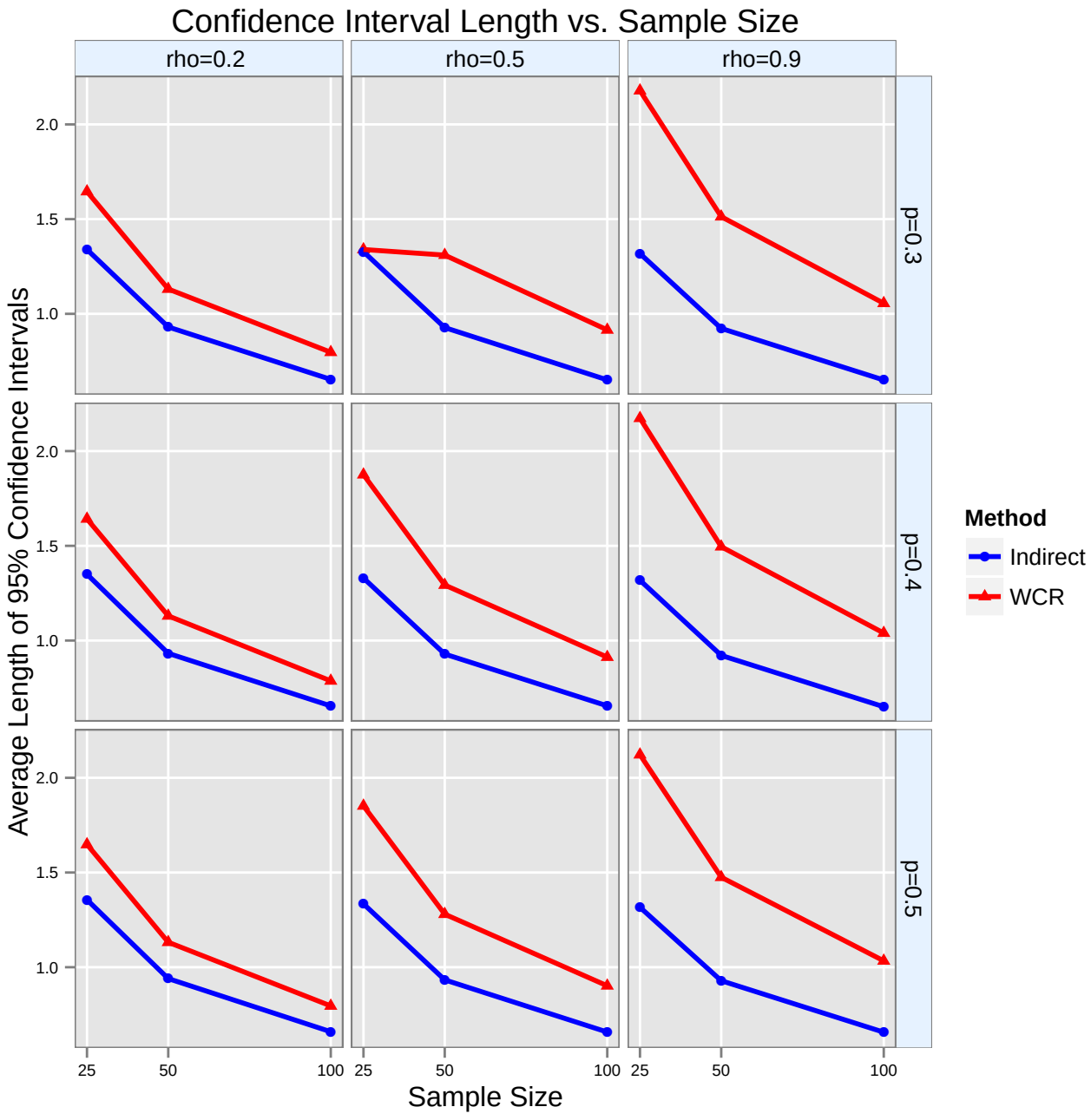

Figure 4.2: The average length of the 95% confidence intervals of indirect regression method and the proposed WCR indirect method under different settings

Table 4.2: Simulation results for β_3 using two indirect methods under unequal variance setting

			WCR				Indirect			
p	rho	n	Bias (%)	RMSE	CP	Length	Bias (%)	RMSE	CP	Length
0.3	0.2	25	0.0031	0.0737	0.921	0.3074	0.0195	0.0722	0.916	0.2491
		50	-0.0163	0.0501	0.911	0.2087	0.0095	0.0501	0.907	0.1724
		100	0.0452	0.0367	0.923	0.1416	0.0144	0.0360	0.904	0.1206
	0.5	25	0.1541	0.0848	0.912	0.3456	0.0294	0.0856	0.844	0.2468
		50	-0.1308	0.0590	0.921	0.2362	-0.1627	0.0594	0.845	0.1730
		100	0.0670	0.0427	0.917	0.1623	0.1219	0.0433	0.834	0.1204
	0.9	25	0.2431	0.1006	0.919	0.3896	0.3676	0.1030	0.772	0.2456
		50	-0.2344	0.0657	0.951	0.2682	-0.2464	0.0684	0.778	0.1706
		100	-0.2970	0.0485	0.939	0.1889	-0.3178	0.0500	0.769	0.1201
0.4	0.2	25	0.1698	0.0789	0.905	0.3235	0.2391	0.0786	0.893	0.2577
		50	-0.2182	0.0528	0.942	0.2111	-0.2088	0.0512	0.915	0.1790
		100	0.0736	0.0010	0.926	0.1449	0.1017	0.0366	0.906	0.1248
	0.5	25	0.3677	0.0855	0.901	0.3534	0.2924	0.0859	0.854	0.2581
		50	0.0169	0.0599	0.925	0.2384	0.0053	0.0601	0.863	0.1793
		100	-0.1058	0.0420	0.944	0.1646	-0.1104	0.0424	0.871	0.1249
	0.9	25	-0.2300	0.1007	0.911	0.3889	-0.1731	0.1040	0.769	0.2539
		50	0.1245	0.0691	0.934	0.2694	0.2601	0.0724	0.786	0.1765
		100	-0.0079	0.0506	0.938	0.1891	0.0769	0.0523	0.749	0.1240
0.5	0.2	25	-0.1614	0.0786	0.921	0.3289	-0.0615	0.0770	0.907	0.2699
		50	0.2207	0.0018	0.925	0.2184	0.1780	0.0018	0.893	0.1863
		100	-0.0299	0.0390	0.929	0.1521	-0.0200	0.0379	0.911	0.1307
	0.5	25	-0.0041	0.0903	0.914	0.3573	0.0840	0.0903	0.859	0.2681
		50	0.0570	0.0005	0.924	0.2432	0.0497	0.0005	0.847	0.1860
		100	0.1731	0.0449	0.924	0.1700	0.1320	0.0453	0.855	0.1307
	0.9	25	-0.0067	0.1004	0.917	0.3987	-0.1417	0.1053	0.795	0.2651
		50	0.0497	-0.0023	0.936	0.2777	0.2338	0.0736	0.801	0.1866
		100	-0.1486	0.0497	0.942	0.1909	-0.1967	0.0514	0.786	0.1297

WCR-the proposed WCR indirect method;
Indirect-the indirect ROC method;
RMSE-square root of mean squared error;
CP-coverage percentage of 95% confidence intervals;
Length- the average of simulated confidence interval lengths.

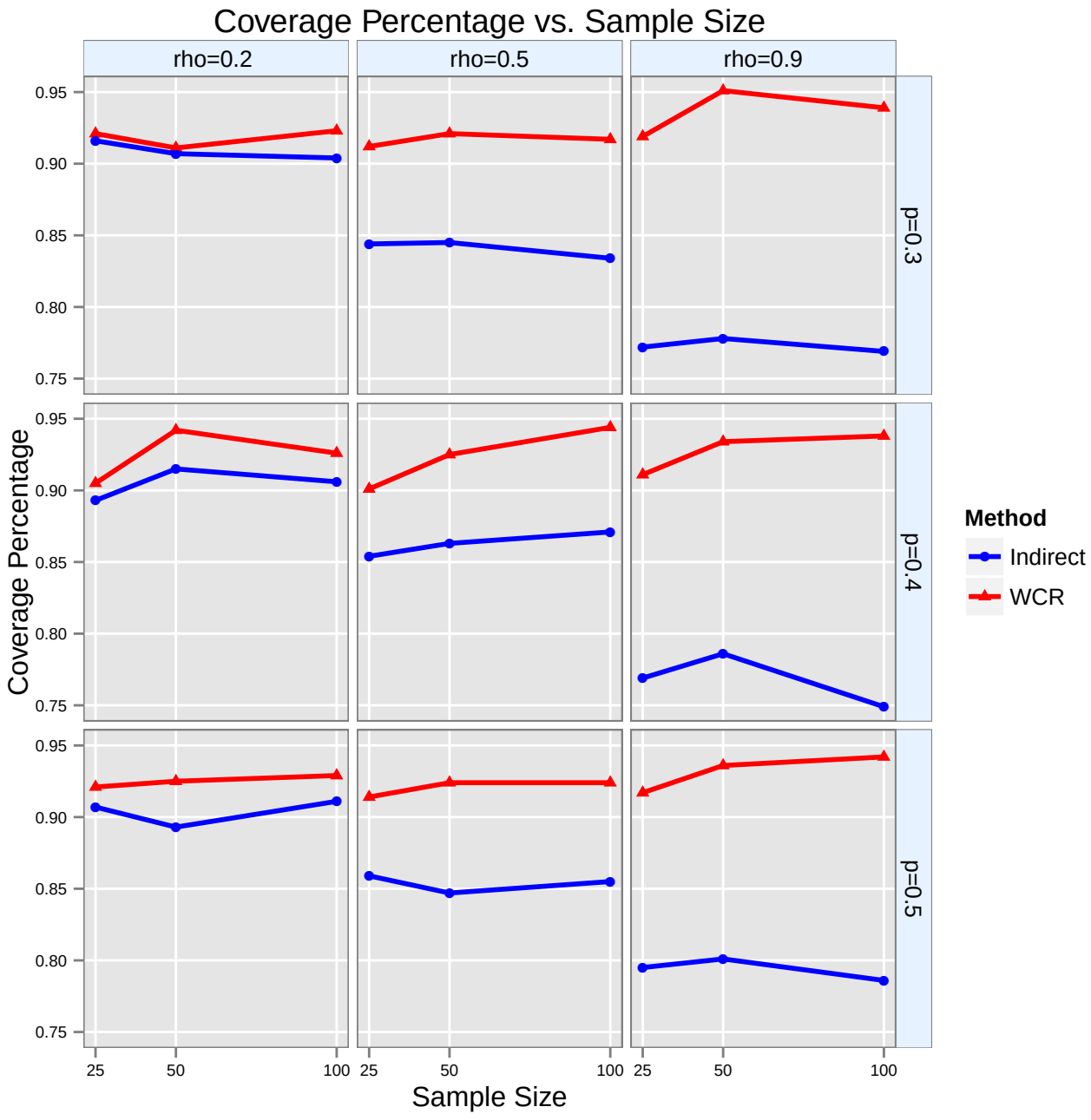

Figure 4.3: The coverage percentage of the 95% confidence intervals of indirect regression method and the proposed WCR indirect method under different settings

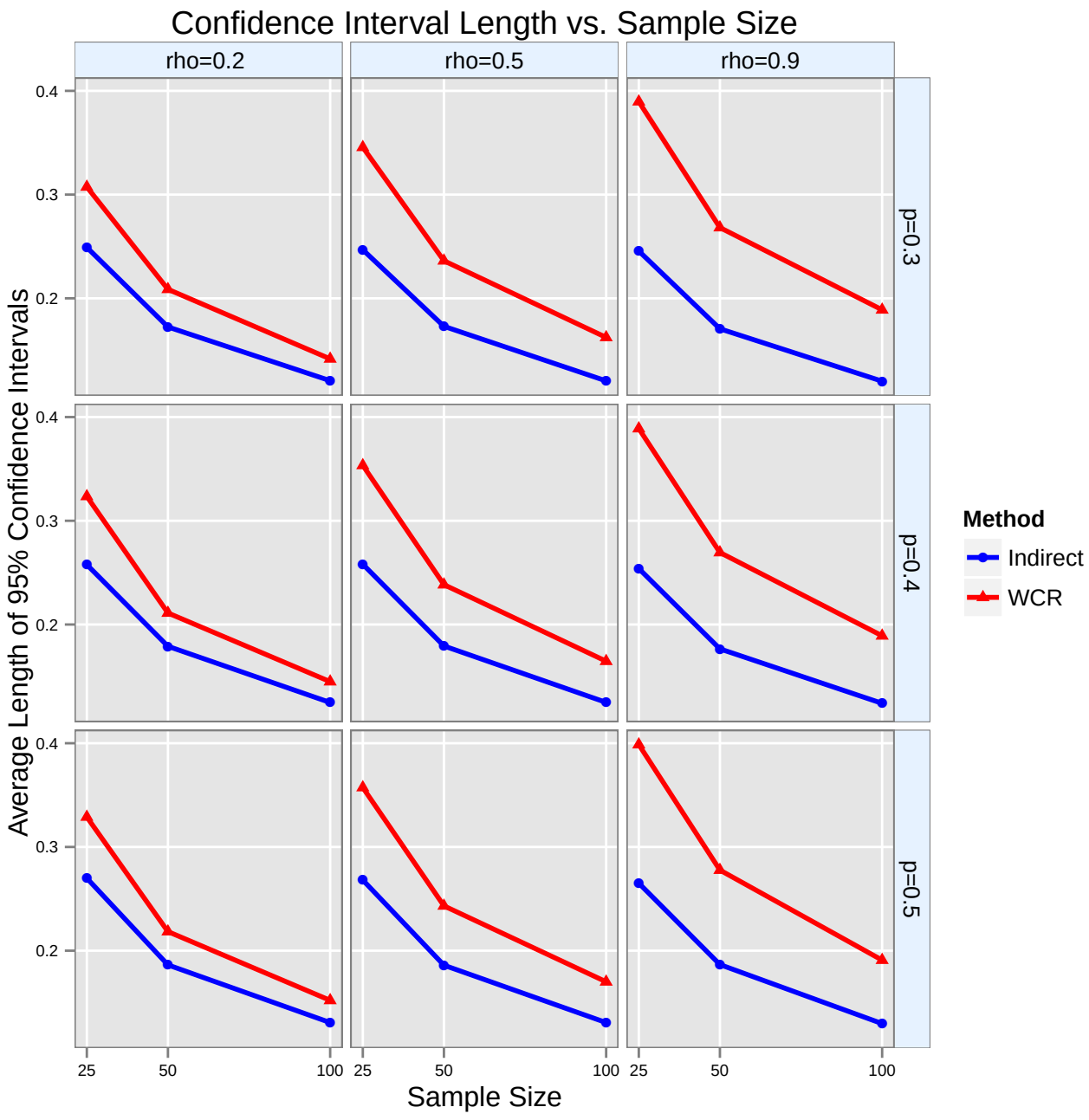

Figure 4.4: The average length of the 95% confidence intervals of indirect regression method and the proposed WCR indirect method under different settings

Table 4.3: Simulation results for $\frac{\beta_3}{\sigma_1}$ using two indirect methods under equal variance setting

			WCR			Indirect		
p	rho	n	Bias (%)	RMSE	CP	Bias (%)	RMSE	CP
0.3	0.2	25	-5.4661	0.0597	0.934	-5.7874	0.0616	0.872
		50	-6.0869	0.0636	0.951	-6.1800	0.0641	0.898
		100	-6.2225	0.0634	0.941	-6.2901	0.0639	0.901
	0.5	25	-5.5387	0.0636	0.925	-5.6706	0.0632	0.802
		50	-5.7045	0.0603	0.976	-5.7702	0.0605	0.787
		100	-6.0284	0.0618	0.961	-6.0800	0.0621	0.793
	0.9	25	-5.8340	0.0695	0.938	-5.6687	0.0672	0.691
		50	-6.2062	0.0664	0.946	-6.1373	0.0652	0.687
		100	-6.2329	0.0646	0.913	-6.2156	0.0643	0.669
0.4	0.2	25	-5.4250	0.0600	0.971	-5.7889	0.0627	0.911
		50	-5.9674	0.0623	0.958	-6.0821	0.0629	0.886
		100	-6.1192	0.0624	0.944	-6.1780	0.0628	0.891
	0.5	25	-5.6920	0.0637	0.953	-5.8725	0.0652	0.784
		50	-5.8032	0.0609	0.934	-5.8456	0.0613	0.793
		100	-6.1203	0.0628	0.939	-6.1293	0.0628	0.776
	0.9	25	-5.8024	0.0669	0.918	-5.6402	0.0656	0.689
		50	-6.1505	0.0664	0.962	-6.0354	0.0651	0.697
		100	-6.1829	0.0641	0.929	-6.1241	0.0636	0.702
0.5	0.2	25	-5.4510	0.0604	0.981	-5.7876	0.0626	0.875
		50	-5.9829	0.0625	0.936	-6.1039	0.0635	0.869
		100	-6.1570	0.0628	0.964	-6.1599	0.0628	0.885
	0.5	25	-5.7440	0.0643	0.955	-5.8816	0.0647	0.787
		50	-6.1508	0.0646	0.928	-6.2093	0.0651	0.769
		100	-6.3342	0.0648	0.911	-6.3487	0.0649	0.795
	0.9	25	-5.9243	0.0693	0.919	-5.7730	0.0687	0.711
		50	-6.0552	0.0648	0.933	-6.0450	0.0649	0.684
		100	-6.1497	0.0639	0.972	-6.0458	0.0632	0.695

WCR-the proposed WCR indirect method;
Indirect-the indirect ROC method;
RMSE-square root of mean squared error;
CP-coverage percentage of 95% confidence intervals.

Table 4.4: Simulation results for $\frac{\beta_3}{\sigma_1}$ using two indirect methods under unequal variance setting

			WCR			Indirect		
p	rho	n	Bias (%)	RMSE	CP	Bias (%)	RMSE	CP
0.3	0.2	25	-5.8095	0.0621	0.915	-6.0516	0.0637	0.901
		50	-5.9657	0.0619	0.921	-6.0847	0.0627	0.892
		100	-6.2135	0.0633	0.923	-6.2515	0.0635	0.887
	0.5	25	-5.7665	0.0633	0.902	-5.8732	0.0635	0.763
		50	-6.0708	0.0637	0.935	-6.1349	0.0640	0.784
		100	-6.1811	0.0633	0.931	-6.1952	0.0633	0.797
	0.9	25	-5.8294	0.0662	0.917	-5.6683	0.0644	0.687
		50	-5.9543	0.0641	0.928	-5.8182	0.0626	0.692
		100	-6.1901	0.0639	0.926	-6.1495	0.0633	0.641
0.4	0.2	25	-5.5864	0.0604	0.913	-5.8699	0.0624	0.915
		50	-6.0807	0.0630	0.909	-6.2073	0.0639	0.887
		100	-6.1204	0.0623	0.934	-6.1865	0.0628	0.903
	0.5	25	-5.6862	0.0628	0.927	-5.7823	0.0633	0.748
		50	-6.0619	0.0638	0.941	-6.1002	0.0639	0.763
		100	-6.0819	0.0624	0.925	-6.0915	0.0623	0.721
	0.9	25	-5.6905	0.0656	0.928	-5.5077	0.0638	0.624
		50	-6.0546	0.0653	0.938	-5.8951	0.0640	0.671
		100	-6.1611	0.0636	0.925	-6.1024	0.0631	0.608
0.5	0.2	25	-5.6912	0.0614	0.937	-5.9279	0.0632	0.898
		50	-5.9261	0.0618	0.933	-6.0680	0.0629	0.887
		100	-6.1403	0.0626	0.926	-6.2171	0.0632	0.893
	0.5	25	-5.6198	0.0622	0.922	-5.7326	0.0631	0.785
		50	-5.9082	0.0625	0.914	-5.9925	0.0632	0.763
		100	-6.1385	0.0629	0.916	-6.1382	0.0629	0.739
	0.9	25	-5.6573	0.0658	0.931	-5.5027	0.0649	0.634
		50	-6.0671	0.0654	0.922	-5.9606	0.0648	0.619
		100	-6.1912	0.0645	0.932	-6.1391	0.0641	0.674

WCR-the proposed WCR indirect method;
Indirect-the indirect ROC method;
RMSE-square root of mean squared error;
CP-coverage percentage of 95% confidence intervals.

Table 4.5: Simulation results for AUC_2 using two indirect methods under equal variance setting

			WCR			Indirect		
p	rho	n	Bias (%)	RMSE	CP	Bias (%)	RMSE	CP
0.3	0.2	25	0.7000	0.0241	0.923	0.8068	0.0238	0.884
		50	1.0094	0.0210	0.934	1.0098	0.0209	0.876
		100	0.8365	0.0177	0.912	0.8517	0.0184	0.893
	0.5	25	0.8246	0.0289	0.925	0.9528	0.0302	0.810
		50	0.6523	0.0225	0.934	0.6591	0.0236	0.823
		100	0.9571	0.0162	0.936	0.9299	0.0157	0.802
	0.9	25	0.7647	0.0347	0.944	0.7806	0.0366	0.724
		50	0.8175	0.0272	0.921	0.7115	0.0285	0.731
		100	0.9702	0.0210	0.937	1.0157	0.0222	0.711
0.4	0.2	25	0.6271	0.0234	0.947	0.7021	0.0236	0.865
		50	0.7925	0.0198	0.957	0.8083	0.0197	0.891
		100	0.8185	0.0156	0.938	0.8294	0.0153	0.889
	0.5	25	0.8881	0.0309	0.964	0.9427	0.0321	0.823
		50	0.7765	0.0236	0.928	0.7550	0.0241	0.812
		100	0.8289	0.0179	0.939	0.8509	0.0185	0.837
	0.9	25	0.7735	0.0339	0.934	0.7260	0.0352	0.768
		50	0.6930	0.0281	0.961	0.7195	0.0303	0.741
		100	0.8727	0.0210	0.921	0.8393	0.0215	0.727
0.5	0.2	25	0.7102	0.0241	0.933	0.7208	0.0236	0.895
		50	0.6934	0.0202	0.921	0.7137	0.0199	0.889
		100	0.8403	0.0148	0.941	0.8963	0.0153	0.893
	0.5	25	0.5977	0.0288	0.934	0.6172	0.0292	0.741
		50	0.8609	0.0224	0.935	0.8250	0.0232	0.813
		100	0.8070	0.0178	0.954	0.7919	0.0183	0.792
	0.9	25	0.7621	0.0342	0.945	0.7417	0.0360	0.681
		50	0.8087	0.0277	0.946	0.8109	0.0296	0.732
		100	0.6844	0.0206	0.941	0.6715	0.0219	0.714

WCR-the proposed WCR indirect method;
Indirect-the indirect ROC method;
RMSE-square root of mean squared error;
CP-coverage percentage of 95% confidence intervals.

Table 4.6: Simulation results for AUC_2 using two indirect methods under unequal variance setting

			WCR			Indirect		
p	rho	n	Bias (%)	RMSE	CP	Bias (%)	RMSE	CP
0.3	0.2	25	-2.0016	0.0650	0.964	1.2391	0.0673	0.871
		50	-1.9873	0.0670	0.921	-1.2080	0.0659	0.863
		100	-1.3203	0.0571	0.967	-0.6907	0.0546	0.911
	0.5	25	-1.9555	0.0730	0.945	-1.2993	0.0777	0.781
		50	-2.0198	0.0740	0.927	-1.2471	0.0759	0.735
		100	-0.9836	0.0676	0.931	-0.6722	0.0670	0.745
	0.9	25	-1.9493	0.0842	0.946	-1.5216	0.0917	0.710
		50	-2.0623	0.0851	0.955	-1.4161	0.0890	0.675
		100	-1.1916	0.0678	0.941	-1.1658	0.0671	0.745
0.4	0.2	25	-1.5927	0.0735	0.945	-0.7532	0.0716	0.856
		50	-1.3639	0.0664	0.938	-0.7089	0.0677	0.901
		100	-0.9492	0.0462	0.962	-0.6097	0.0458	0.893
	0.5	25	-2.5139	0.0829	0.937	-1.4631	0.0823	0.871
		50	-1.3516	0.0786	0.968	-0.8475	0.0807	0.875
		100	-0.9680	0.0531	0.924	-0.7311	0.0539	0.865
	0.9	25	-2.6385	0.0947	0.948	-1.6462	0.0955	0.768
		50	-1.3253	0.0888	0.951	-0.9799	0.0937	0.712
		100	-1.9351	0.0815	0.953	-1.3459	0.0858	0.645
0.5	0.2	25	-2.9234	0.0794	0.955	-1.8001	0.0769	0.895
		50	-1.2909	0.0684	0.914	-0.5812	0.0676	0.871
		100	-1.6530	0.0632	0.941	-1.0884	0.0604	0.912
	0.5	25	-2.9560	0.0859	0.931	-1.8928	0.0860	0.841
		50	-1.2417	0.0763	0.922	-0.5671	0.0781	0.787
		100	-1.8732	0.0736	0.938	-1.2513	0.0757	0.805
	0.9	25	-3.0579	0.0964	0.945	-2.1563	0.1001	0.831
		50	-1.1757	0.0855	0.915	-0.6633	0.0900	0.746
		100	-0.6392	0.0775	0.925	-0.2918	0.0800	0.763

WCR-the proposed WCR indirect method;
Indirect-the indirect ROC method;
RMSE-square root of mean squared error;
CP-coverage percentage of 95% confidence intervals.

Table 4.7: Simulation results for AUC_5 using two indirect methods under equal variance setting

			WCR			Indirect		
p	rho	n	Bias (%)	RMSE	CP	Bias (%)	RMSE	CP
0.3	0.2	25	1.0016	0.0207	0.971	1.1424	0.0216	0.899
		50	1.2074	0.0184	0.919	1.2780	0.0188	0.852
		100	1.3296	0.0163	0.937	1.3622	0.0166	0.901
	0.5	25	1.0469	0.0252	0.966	1.1505	0.0264	0.877
		50	1.1187	0.0209	0.937	1.1780	0.0217	0.791
		100	1.3237	0.0181	0.924	1.3524	0.0185	0.757
	0.9	25	2.5203	0.0291	0.965	1.2802	0.0302	0.713
		50	1.2145	0.0241	0.912	1.2043	0.0251	0.732
		100	1.3599	0.0201	0.951	1.3690	0.0207	0.663
0.4	0.2	25	1.0139	0.0222	0.953	1.1588	0.0225	0.911
		50	1.2591	0.0189	0.926	1.3758	0.0197	0.878
		100	1.2346	0.0156	0.914	1.2891	0.0162	0.894
	0.5	25	1.1299	0.0253	0.961	1.2104	0.0267	0.731
		50	1.0935	0.0211	0.926	1.1389	0.0221	0.765
		100	1.1821	0.0174	0.932	1.1760	0.0176	0.777
	0.9	25	0.9608	0.0280	0.942	0.9756	0.0289	0.751
		50	1.0828	0.0242	0.942	1.0468	0.0253	0.656
		100	1.2072	0.0194	0.938	1.2376	0.0200	0.577
0.5	0.2	25	1.0714	0.0220	0.926	1.2385	0.0230	0.874
		50	1.1060	0.0185	0.953	1.2116	0.0192	0.806
		100	1.3018	0.0164	0.959	1.3479	0.0169	0.856
	0.5	25	1.0690	0.0253	0.921	1.1520	0.0264	0.772
		50	1.2191	0.0221	0.966	1.2775	0.0229	0.733
		100	1.2071	0.0174	0.912	1.1944	0.0177	0.765
	0.9	25	1.1903	0.0288	0.926	1.1763	0.0314	0.664
		50	1.1234	0.0240	0.961	1.1148	0.0251	0.674
		100	1.2663	0.0192	0.921	1.2528	0.0201	0.664

WCR-the proposed WCR indirect method;
Indirect-the indirect ROC method;
RMSE-square root of mean squared error;
CP-coverage percentage of 95% confidence intervals.

Table 4.8: Simulation results for AUC_5 using two indirect methods under unequal variance setting

			WCR			Indirect		
p	rho	n	Bias (%)	RMSE	CP	Bias (%)	RMSE	CP
0.3	0.2	25	-1.8284	0.0328	0.974	-1.1803	0.0288	0.915
		50	-1.4182	0.0250	0.911	-1.0836	0.0225	0.873
		100	-1.0370	0.0174	0.934	-0.8498	0.0161	0.913
	0.5	25	-1.6712	0.0335	0.930	-1.1191	0.0309	0.861
		50	-1.2887	0.0265	0.942	-1.0288	0.0257	0.858
		100	-1.1919	0.0206	0.929	-1.0345	0.0197	0.789
	0.9	25	-1.6691	0.0392	0.941	-1.2931	0.0379	0.702
		50	-1.1123	0.0287	0.896	-0.8698	0.0283	0.730
		100	-1.1500	0.0224	0.910	1.0162	0.0224	0.654
0.4	0.2	25	-1.8440	0.0331	0.932	-1.1965	0.0295	0.899
		50	2.8685	0.0252	0.933	-1.1855	0.0232	0.869
		100	-1.1833	0.0189	0.906	1.0091	0.0177	0.980
	0.5	25	-1.8064	0.0365	0.941	-1.3422	0.0347	0.696
		50	-1.4483	0.0286	0.944	1.1427	0.0272	0.756
		100	-1.1438	0.0199	0.913	1.0089	0.0194	0.810
	0.9	25	-1.7695	0.0389	0.902	-1.3031	0.0379	0.724
		50	-1.5046	0.0328	0.927	1.2421	0.0321	0.641
		100	-1.1331	0.0222	0.952	-1.0128	0.0222	0.575
0.5	0.2	25	-1.6361	0.0336	0.944	1.0450	0.0299	0.919
		50	-1.5364	0.0269	0.976	-1.1162	0.0239	0.901
		100	-1.0383	0.0188	0.948	-0.8622	0.0178	0.879
	0.5	25	-1.7873	0.0379	0.945	1.2395	0.0361	0.704
		50	-1.2371	0.0256	0.915	-0.9033	0.0242	0.816
		100	-1.0657	0.0205	0.937	-0.8831	0.0195	0.776
	0.9	25	-1.6382	0.0375	0.885	1.1146	0.0372	0.702
		50	-1.2278	0.0309	0.960	-0.9619	0.0308	0.680
		100	-1.1947	0.0231	0.936	-1.0530	0.0231	0.671

WCR-the proposed WCR indirect method;
Indirect-the indirect ROC method;
RMSE-square root of mean squared error;
CP-coverage percentage of 95% confidence intervals.

Table 4.9: Simulation results for AUC_9 using two indirect methods under equal variance setting

p	rho	n	WCR			Indirect		
			Bias (%)	RMSE	CP	Bias (%)	RMSE	CP
0.3	0.2	25	0.1980	0.0096	0.964	0.4628	0.0098	0.901
		50	0.4645	0.0079	0.953	0.6151	0.0087	0.912
		100	0.5344	0.0070	0.933	0.6041	0.0075	0.898
	0.5	25	0.3149	0.0104	0.911	0.5010	0.0111	0.835
		50	0.3967	0.0089	0.923	0.5051	0.0094	0.842
		100	0.5290	0.0078	0.964	0.5789	0.0084	0.851
	0.9	25	0.1361	0.0136	0.931	0.1951	0.0143	0.797
		50	0.4066	0.0110	0.912	0.4666	0.0114	0.789
		100	0.5459	0.0085	0.918	0.5639	0.0090	0.756
0.4	0.2	25	0.1766	0.0100	0.927	0.4413	0.0101	0.878
		50	0.4145	0.0082	0.926	0.5693	0.0088	0.881
		100	0.5017	0.0067	0.934	0.5762	0.0072	0.868
	0.5	25	0.1883	0.0114	0.923	0.3924	0.0117	0.831
		50	0.3722	0.0091	0.941	0.4968	0.0097	0.854
		100	0.5399	0.0080	0.949	0.5994	0.0084	0.828
	0.9	25	0.1527	0.0141	0.954	0.2674	0.0145	0.787
		50	0.4501	0.0102	0.937	0.4832	0.0108	0.742
		100	0.5079	0.0084	0.957	0.5401	0.0088	0.758
0.5	0.2	25	0.2039	0.0092	0.913	0.4782	0.0099	0.921
		50	0.3932	0.0078	0.948	0.5617	0.0085	0.873
		100	0.5188	0.0070	0.956	0.6020	0.0076	0.895
	0.5	25	0.2012	0.0116	0.926	0.3973	0.0119	0.846
		50	0.3791	0.0087	0.962	0.5037	0.0095	0.827
		100	0.4894	0.0075	0.934	0.5424	0.0081	0.839
	0.9	25	0.2338	0.0131	0.955	0.3267	0.0145	0.775
		50	0.4511	0.0109	0.915	0.4962	0.0116	0.764
		100	0.5598	0.0085	0.942	0.5980	0.0092	0.725

WCR-the proposed WCR indirect method;
Indirect-the indirect ROC method;
RMSE-square root of mean squared error;
CP-coverage percentage of 95% confidence intervals.

Table 4.10: Simulation results for AUC_9 using two indirect methods under unequal variance setting

			WCR			Indirect		
p	rho	n	Bias (%)	RMSE	CP	Bias (%)	RMSE	CP
0.3	0.2	25	-1.3265	0.0186	0.912	-0.6213	0.0126	0.798
		50	-0.9229	0.0133	0.973	-0.5021	0.0098	0.919
		100	-0.7192	0.0102	0.966	-0.4267	0.0079	0.926
	0.5	25	-1.3376	0.0202	0.899	-0.7017	0.0152	0.725
		50	-0.8852	0.0137	0.986	-0.5379	0.0112	0.812
		100	-0.6813	0.0107	0.967	-0.4316	0.0087	0.838
	0.9	25	-1.3613	0.0226	0.921	-0.8434	0.0189	0.644
		50	-0.9017	0.0152	0.961	-0.6177	0.0136	0.523
		100	-0.6962	0.0115	0.943	-0.4983	0.0099	0.416
0.4	0.2	25	-1.2584	0.0188	0.965	-0.5316	0.0122	0.913
		50	1.5248	0.0117	0.966	-0.4274	0.0087	0.891
		100	-0.6913	0.0105	0.931	-0.4214	0.0083	0.921
	0.5	25	-1.1979	0.0185	0.968	-0.5599	0.0131	0.784
		50	-0.8278	0.0129	0.916	-0.4957	0.0102	0.723
		100	-0.8423	0.0128	0.932	-0.5505	0.0102	0.718
	0.9	25	-1.1958	0.0204	0.948	-0.6560	0.0161	0.623
		50	-0.8176	0.0141	0.957	-0.5528	0.0121	0.691
		100	-0.6445	0.0129	0.934	-0.4518	0.0112	0.532
0.5	0.2	25	-1.6464	0.0250	0.926	-0.8488	0.0183	0.885
		50	-0.8633	0.0137	0.986	-0.4679	0.0109	0.919
		100	-0.7743	0.0115	0.953	-0.4920	0.0093	0.865
	0.5	25	-1.3486	0.0204	0.954	-0.6787	0.0148	0.712
		50	-0.8517	0.0133	0.959	-0.4961	0.0107	0.744
		100	-0.7866	0.0116	0.938	-0.5480	0.0097	0.756
	0.9	25	-1.2711	0.0213	0.966	-0.7580	0.0173	0.402
		50	-0.9008	0.0149	0.959	-0.6422	0.0137	0.704
		100	-0.6747	0.0106	0.947	-0.4685	0.0091	0.732

WCR-the proposed WCR indirect method;
Indirect-the indirect ROC method;
RMSE-square root of mean squared error;
CP-coverage percentage of 95% confidence intervals.

4.2.2 Simulation Study for WCR Indirect Regression Methods

For the simulated clustered ROC data associated with continuous covariate x_1, The proposed WCR direct methods are used as well as traditional indirect regression method. We set the pairing margin $\delta = \infty$ so that all the pairs can be included in the model

$$ROC_{x_D,x_{\bar{D}}}(u) = \Phi\{\alpha_0 + \alpha_1\Phi^{-1}(u) + \beta_1 x_D + \beta_2(x_D - x_{\bar{D}})\}. \tag{4.51}$$

The resulting AUC is given by,

$$AUC_{x_D,x_{\bar{D}}}(u) = \Phi^{-1}\{\beta_0 + \beta_1 x_D + \beta_2(x_D - x_{\bar{D}})\}. \tag{4.52}$$

We also generate clustered ROC data with a categorical covariate $x_1 = 1, 2, 3, 4$ and 5. We create all the pairs within each level and fit the models to estimate the ROC curves and the AUC by

$$ROC_{x_D,x_{\bar{D}}}(u) = \Phi\{\alpha_0 + \alpha_1\Phi^{-1}(u) + \beta_1 x_D\}, \tag{4.53}$$

and

$$AUC_{x_D,x_{\bar{D}}}(u) = \Phi^{-1}\{\beta_0 + \beta_1 x_D\}. \tag{4.54}$$

The parameter estimator $\hat{\beta}_1$ and the AUC estimator when $x_1 = 1$, $\widehat{AUC}_{x_1=1}$ are obtained. Biases and square root of mean squared errors under various scenarios are shown in the tables.

Table 4.11, 4.12, and 4.13 show the simulation results to compare the proposed WCR indirect regression methods with traditional indirect method using β_1 and $AUC_{x_1=1}$ under continues data and ordinal data. The biases obtained by the proposed methods are very small. This indicates that the proposed WCR methods have a good performance on clustered ROC data associated with covariate X. Note that, the traditional method provides similar bias and RMSE but the two methods are on difference levels. The WCR methods are on a patient/subject level and the traditional method is on the location level. We do not report the coverage percentage of 95% confidence interval since the bootstrap method did not work well to estimate the variance of β_1 and the variance of $AUC_{x_1=1}$.

Further research on estimating the variance is needed for this WCR methods.

Table 4.11: Simulation results for β_1 using two direct methods under continuous data setting

			WCR		Direct	
p	rho	n	Bias (%)	RMSE	Bias (%)	RMSE
0.3	0.2	25	3.3905	0.0751	0.8074	0.0574
		50	2.7895	0.0658	0.6359	0.0524
		100	1.4871	0.0509	0.3217	0.0442
	0.5	25	4.4960	0.1032	1.9697	0.0817
		50	2.4036	0.0755	0.9539	0.0676
		100	1.4687	0.0585	0.3336	0.0533
	0.9	25	2.3745	0.1006	1.0071	0.0968
		50	2.2644	0.0903	1.4482	0.0857
		100	1.9500	0.0752	1.4003	0.0722
0.4	0.2	25	4.1896	0.0796	1.3721	0.0597
		50	2.6498	0.0631	0.5102	0.0518
		100	1.9822	0.0550	0.6539	0.0489
	0.5	25	3.4862	0.0928	1.1125	0.0777
		50	2.3407	0.0710	0.5359	0.0637
		100	2.1212	0.0601	1.0164	0.0541
	0.9	25	3.6568	0.1195	2.2070	0.1079
		50	3.0022	0.0928	2.1884	0.0896
		100	2.1327	0.0789	1.5601	0.0760
0.5	0.2	25	3.3933	0.0809	0.6523	0.0636
		50	2.6191	0.0644	0.6712	0.0532
		100	2.0545	0.0523	0.7630	0.0452
	0.5	25	3.9982	0.0947	1.5693	0.0783
		50	2.7592	0.0766	1.0361	0.0682
		100	2.0294	0.0615	0.9549	0.0572
	0.9	25	4.0270	0.1223	2.4030	0.1094
		50	2.3574	0.0916	1.5129	0.0913
		100	1.6858	0.0709	1.1866	0.0718

WCR-the proposed WCR indirect method;
Direct-the direct ROC method;
RMSE-square root of mean squared error;

Table 4.12: Simulation results for β_3 using two direct methods under ordinal data setting

			WCR		Direct	
p	rho	n	Bias (%)	RMSE	Bias (%)	RMSE
0.3	0.2	25	0.1082	0.1774	-0.7181	0.1722
		50	0.8929	0.0557	-5.4982	0.0759
		100	0.5103	0.0372	-5.6146	0.0676
	0.5	25	1.6048	0.2189	1.1021	0.2221
		50	0.2899	0.0637	-5.8925	0.0869
		100	0.5025	0.0433	-5.8461	0.0717
	0.9	25	0.3177	0.1552	-0.0736	0.1533
		50	1.5492	0.0746	-4.2181	0.0879
		100	0.7934	0.0511	-4.9839	0.0716
0.4	0.2	25	2.7662	0.2004	1.9246	0.2023
		50	1.0559	0.0609	-5.5751	0.0804
		100	0.4791	0.0371	-5.4747	0.0664
	0.5	25	-0.1018	0.2336	-0.0142	0.244
		50	0.7705	0.0633	-5.2361	0.0826
		100	0.1338	0.0444	-5.9394	0.0755
	0.9	25	0.3224	0.1589	-0.1953	0.1569
		50	0.7925	0.0461	-5.5946	0.0723
		100	-0.2469	0.0516	-5.8739	0.0801
0.5	0.2	25	1.1535	0.1415	0.2504	0.1358
		50	0.9302	0.0441	-5.2282	0.0688
		100	0.4687	0.0387	-5.3873	0.0651
	0.5	25	2.5461	0.1711	2.3547	0.1786
		50	0.5766	0.0521	-4.9761	0.0708
		100	-0.0821	0.0419	-5.6777	0.0757
	0.9	25	1.0082	0.2112	0.7919	0.2246
		50	0.6114	0.0639	-5.4357	0.0878
		100	0.6017	0.0569	-5.2836	0.0799

WCR-the proposed WCR indirect method;
Direct-the direct ROC method;
RMSE-square root of mean squared error;

Table 4.13: Simulation results for $AUC_{x_1=1}$ using two direct methods under ordinal data setting

			WCR		Direct	
p	rho	n	Bias (%)	RMSE	Bias (%)	RMSE
0.3	0.2	25	-0.7586	0.077	-0.5594	0.0729
		50	0.0131	0.0613	0.2083	0.0591
		100	0.0149	0.0487	0.1731	0.0482
	0.5	25	-0.3097	0.0794	-0.1871	0.0755
		50	-0.3865	0.0748	-0.1539	0.0743
		100	0.0125	0.0553	-0.0816	0.0536
	0.9	25	-0.1666	0.1159	-0.1616	0.1164
		50	-0.0627	0.0969	0.1857	0.0973
		100	-0.4054	0.0651	-0.4508	0.0666
0.4	0.2	25	-1.6225	0.0798	-1.2971	0.0735
		50	-0.5851	0.0687	-0.3946	0.0667
		100	0.1678	0.0501	0.1431	0.0481
	0.5	25	0.3678	0.0797	0.4377	0.0798
		50	-0.0564	0.0727	-0.0267	0.0726
		100	-0.4418	0.0555	-0.3444	0.0567
	0.9	25	-0.7141	0.1055	-0.7796	0.1085
		50	-0.3936	0.0961	-0.2848	0.0997
		100	0.2325	0.0652	0.2201	0.0654
0.5	0.2	25	0.0518	0.0736	0.3007	0.0744
		50	-0.4993	0.0666	-0.1496	0.0652
		100	0.0671	0.0468	0.2549	0.0469
	0.5	25	-0.4788	0.0791	-0.2581	0.0822
		50	-0.9019	0.0814	-1.0971	0.0838
		100	-0.6744	0.0526	-0.4888	0.0561
	0.9	25	-0.4978	0.0961	-0.2091	0.1027
		50	0.4204	0.0927	0.9662	0.1011
		100	0.0018	0.0604	0.1766	0.0627

WCR-the proposed WCR indirect method;
Direct-the direct ROC method;
RMSE-square root of mean squared error;

Chapter 5: Conclusion and Future Research

In this dissertation, we propose within cluster resampling methods to deal with clustered ROC data. They have been shown to be valid analysis methods to estimate the ROC curve and the ROC summary measures. We applied the within cluster resampling methods on evaluating one ROC curve, comparing two ROC curves and estimating covariate adjusted ROC curves. The methods provide unbiased estimators as well as valid variance estimators since they can deal with the within cluster correlation. We illustrate how well the proposed methods perform through extensive simulation studies in Sections 2, 3 and 4.

Compared to the current methods, the within cluster resampling methods have many advantages. First, the WCR methods give us a general framework on estimating the ROC curve using the clustered ROC data. We can obtain all the ROC measures including the AUC, the pAUC, the TPR at a fixed FPR, and etc. The Obuchowski's method can only estimate the AUC. It cannot estimate the ROC curves, the pAUC or TPR at a fixed FPR. The Li and Zhou's method (Li and Zhou 2008) cannot adjust for ties in ordinal data since they use a simulated standard normal distribution to estimate the variance. Second, the existing methods for clustered ordinal data yield a rough ROC curve but the WCR method can generate a smoother curve so that more accurate ROC measures, including the pAUC and the TPR at a fixed FPR, can be obtained. Third, the WCR method provides a more flexible way to estimate the ROC curves. For each resampled dataset, we can choose among the parametric, the nonparametric or the semiparametric methods. If the normal assumption stands, the parametric method is preferred because it is easy and accurate. If the normal assumption is violated, the nonparametric method and semiparametric method should be employed. Fourth, to the best of our knowledge, methods are not available to deal with clustered ROC data with covariates. The WCR method is the first and only method to estimate the covariate adjusted ROC curves for the clustered ROC data. The WCR indirect regression and the WCR direct regression method are proposed to estimate the ROC curve associated with covariates. Sixth, the simulation results also

show that WCR methods can account for the informative cluster size since it weighs each cluster equally. In other methods, the clusters with a large number of observations may contribute more. The coverage percentages are close to the nominal level under different settings. Finally, the WCR methods give the subject/patient level ROC estimators while the existing methods give the observation/location level ROC estimators. The choice of those methods depends on the objective of the study, if the study is to measure how accurate the biomarker performs on the patients, the WCR methods should be employed; if the study is to measure the biomarker diagnostic accuracy on the locations from the patients, the existing methods should be employed.

Although the proposed methods have many advantages, they are more computationally intensive to obtain estimators comparing to Obuchowski's methods. When the cluster size is large, the proposed methods require a large number of resamplings. For the proposed WCR methods in Chapters 2 and 3, the variance estimators have explicit forms, the simulation was not very slow. However, the variance estimators have no explicit forms when estimating the covariate adjusted ROC curves. In that case, the bootstrapped variance should be used. But it can be more computationally intensive if we use both the WCR method and the bootstrap method.

Future research work includes the derivation of the asymptotic normality of the WCR AUC estimator. The Central Limit Theorem, the Cauchy-Schwarz Inequality and conditions may be applied. We will also derive the consistency of the variance of the WCR AUC estimator. The conditional variance representation will be used. The Markov's Theorem may be applied. The second future research topic is to determine the adequate number of resamplings to achieve a stable parameter and variance estimates. We will investigate this topic through different numbers of resamplings under different sample sizes. For each sample size and simulation setting, the bias and RMSE are expected to decrease as the number of resamplings increases. The adequate number of resamplings will be determined when the change of bias and RMSE are in an acceptance region. The third future topic is the application of the WCR method to estimate other ROC summary measures, including the pAUC and the TPR at a fixed FPR as well as the asymptotic normality of the corresponding WCR estimators and consistency of the variance of the corresponding WCR estimators. Also, informative cluster sizes have an important cluster effect in clustered ROC data, which is another interesting

area to investigate. The informative cluster size might have a certain distribution and it may affect the ROC estimator if we use traditional methods. The WCR methods can weigh all the clusters equally so that they can handle the informative cluster size.

Appendix A: Data Description for the Examples in Section 2.3

A.1 First Data Example in Section 2.3

This dataset is from Rosner, Glynn, and Lee (2003). They recruited 497 patients who were randomized to three groups: each eye of the patients received the same treatment with an active drug in Group 1; both eyes of the patients received the same treatment with a placebo in Group 2; both eyes of each patient received the placebo and the other eye received the active drug in Group 3. The patients were examined at 1 year and then at 9 months intervals, up to 48 months. They had a final visit at the end of the trial. Sixteen patients did not follow up and three patients were miss at the baseline. So the analysis used 478 patients, of whom 237 were randomized to the active drug and 241 to the placebo. The itching scores were measured at the third visit, which were from 0 (no itch at all) to 4 (severe itch) in an increments of 0.5. The resulting data are clustered with a fixed cluster size two. The number of itching scores that are from active drug treatment can be zero, one or two. The sample data used is a subset of the entire data.

Figure A.1 displays the histogram of the diseased and nondiseased ratings. The left panel shows the histogram of the diseased ratings. The right panel shows the histogram of the nondiseased ratings.

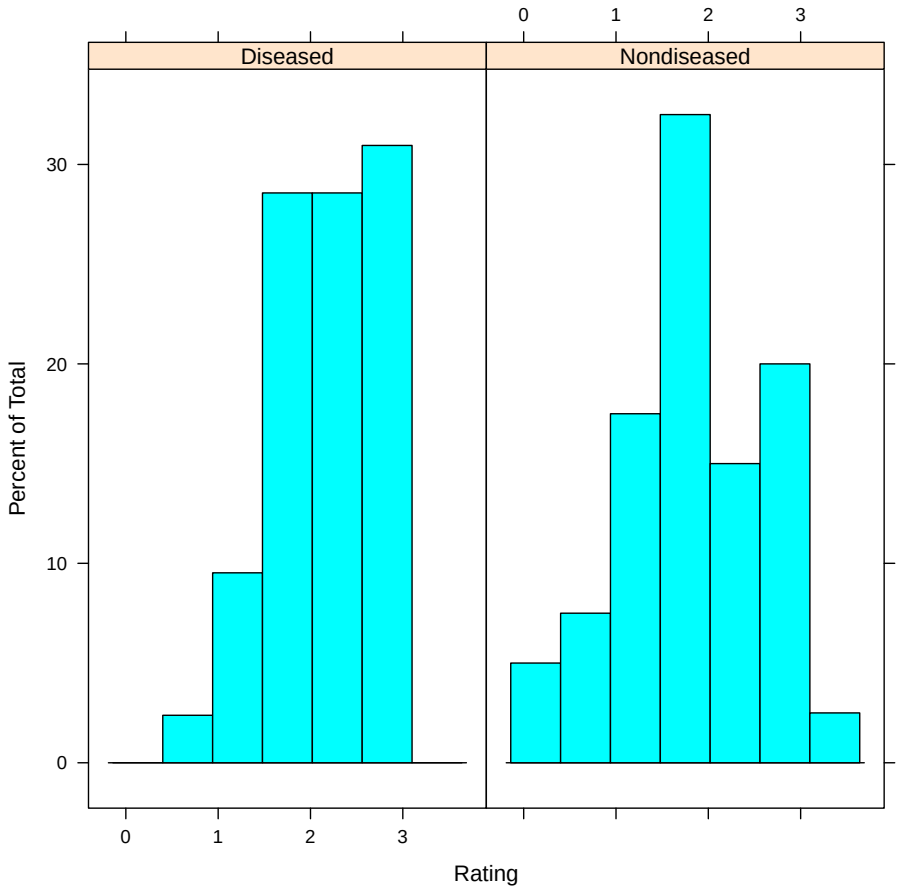

Figure A.1: The left panel shows the histogram of the diseased ratings. The right panel shows the histogram of the nondiseased ratings.

A.2 Second Data Example in Section 2.3

The second data set is from Li and Zhou (2008). In order to detect visual field deterioration in glaucoma patients, Jiang (2005) developed a Bayesian hierarchical modeling method to predict the probability of the early diagnosis of glaucomatous progression using longitudinal visual field image data. The patients can either have none, one or two abnormal eye ratings. This generates the clustered data with cluster size of two.

Figure A.2 displays the histogram of the probability of the early diagnosis of glaucomatous progression for the diseased and nondiseased groups. The left panel shows the histogram of the probability of the early diagnosis of glaucomatous progression for the diseased ratings. The right panel shows the histogram of the probability of the early diagnosis of glaucomatous progression for the nondiseased ratings. Figure A.3 displays the histogram of the probability of the early diagnosis of glaucomatous progression for the left and right eye ratings. The left panel shows the histogram of the early diagnosis of glaucomatous progression for the left eyes. The right panel shows the histogram of the early diagnosis of glaucomatous progression for the right eyes.

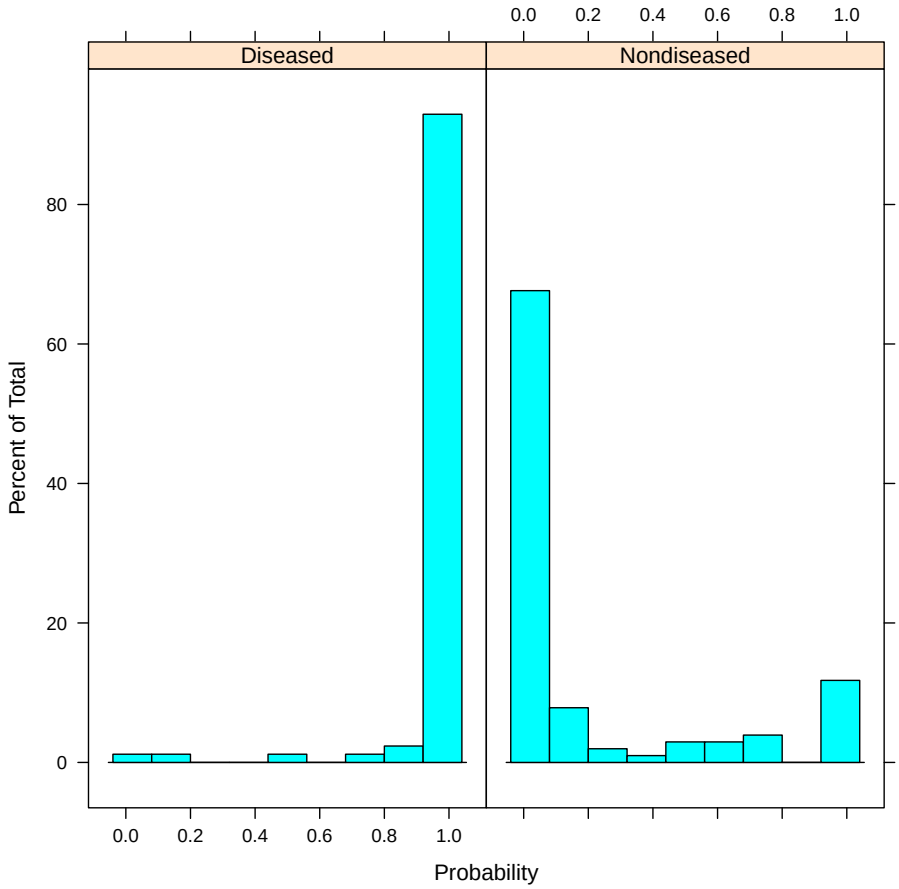

Figure A.2: The left panel shows the histogram of the probability of the early diagnosis of glaucomatous progression for the diseased ratings. The right panel shows the histogram of the probability of the early diagnosis of glaucomatous progression for the nondiseased ratings.

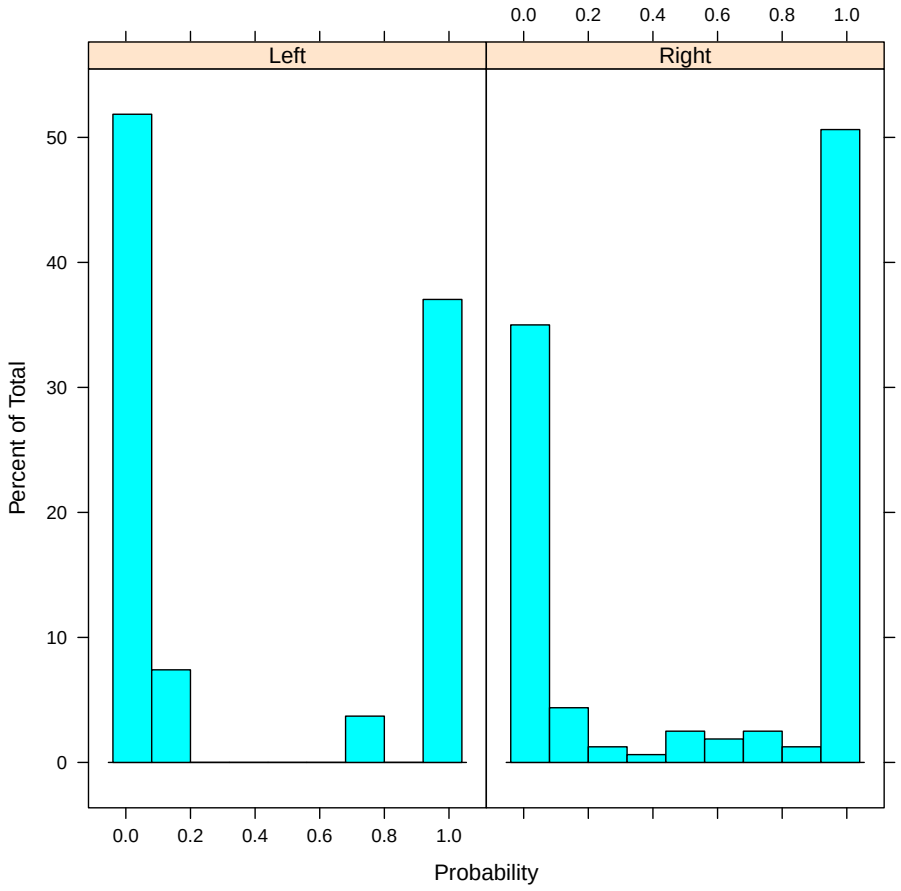

Figure A.3: The left panel shows the histogram of the early diagnosis of glaucomatous progression for the left eyes. The right panel shows the histogram of the early diagnosis of glaucomatous progression for the right eyes.

Appendix B: Simulation Settings

B.1 Simulation Settings for Section 2.2

Let I_1 and I_0 denote the number of clusters in the diseased group and the nondiseased group. We let the two groups have the same number of clusters, so that $I_1 = I_0 = I/2$. The clusters in the diseased group have a cluster size $m_i = 3$ with probability p and a cluster size $m_i = 6$ with probability $1 - p$, where as the clusters in the nondiseased group have a cluster size $n_j = 2$ with probability $1 - p$ and a cluster size $n_j = 5$ with probability p. We simulate 1000 clustered ROC data from normal and lognormal distributions, respectively:

1. $T^d \sim N(\mu_{T^d}, \mathbf{\Sigma}_{T^d})$ and $T^{\bar{d}} \sim N(\mu_{T^{\bar{d}}}, \mathbf{\Sigma}_{T^{\bar{d}}})$, where $\boldsymbol{\mu}_{T^d} = (1, 1, 0)$ when $m_i = 3$ and $\boldsymbol{\mu}_{T^d} = (1, 1, 1, 1, 1, 0)$ when $m_i = 6$, $\boldsymbol{\mu}_{T^{\bar{d}}} = (0, 0)$ when $n_j = 2$ and $\boldsymbol{\mu}_{T^{\bar{d}}} = (0, 0, 0, 0, 0)$ when $n_j = 5$. The variance-covariance matrix $\mathbf{\Sigma}_{T^d}$ is a $m_i \times m_i$ matrix with diagonal elements equal to 1 and correlation coefficients equal to ρ and $\mathbf{\Sigma}_{T^{\bar{d}}}$ is a $n_j \times n_j$ matrix with diagonal elements equal to 1 and correlation coefficients equal to ρ

2. $T^d \sim LogNormal(\mu_{T^d}, \mathbf{\Sigma}_{T^d})$ and $T^{\bar{d}} \sim LogNormal(\mu_{T^{\bar{d}}}, \mathbf{\Sigma}_{T^{\bar{d}}})$, with the same settings on μ_{T^d}, $\mathbf{\Sigma}_{T^d}$, $\mu_{T^{\bar{d}}}$, $\mathbf{\Sigma}_{T^{\bar{d}}}$, m_i, n_j and ρ.

We let p, the informative cluster size correlation, be 0.3, 0.4 and 0.5. Note that when $p \neq 0.5$, the cluster size is different between the two groups. Under each setting, we let ρ, the within-cluster correlation, be 0.2, 0.5, 0.9 and $I/2$, the number of clusters in each group, be 25, 50 and 100.

B.2 Simulation Settings for Section 3.2

Let $I_{\ell 1}$ and $I_{\ell 0}$ denote the number of clusters in the diseased group and the nondiseased group for the ℓth biomarker, and $I_{11} = I_{21}$, $I_{10} = I_{20}$. We let the two groups have the same number of clusters, so that $I_{\ell 1} = I_{\ell 0} = I/2$. For the ℓth biomarker, the clusters in the diseased group have a cluster size $m_{\ell i} = 3$ with probability p and a cluster size $m_{\ell i} = 6$ with probability $1 - p$, where as

the clusters in the nondiseased group have a cluster size $n_{\ell j} = 2$ with probability $1-p$ and a cluster size $n_{\ell j} = 5$ with probability p. We simulate 1000 clustered ROC data from normal and lognormal distributions, respectively:

1. $T_\ell^d \sim N(\mu_{T_\ell^d}, \mathbf{\Sigma}_{T_\ell^d})$ and $T_\ell^{\bar{d}} \sim N(\mu_{T_\ell^{\bar{d}}}, \mathbf{\Sigma}_{T_\ell^{\bar{d}}})$, where $\boldsymbol{\mu}_{T_1^d} = (1,1,0)$ and $\boldsymbol{\mu}_{T_2^d} = (0.7, 0.7, 0)$ when $m_{\ell i} = 3$ and $\boldsymbol{\mu}_{T_1^d} = (1,1,1,1,1,0)$ and $\boldsymbol{\mu}_{T_2^d} = (0.7, 0.7, 0.7, 0.7, 0)$ when $m_{\ell i} = 6$, $\boldsymbol{\mu}_{T_\ell^{\bar{d}}} = (0,0)$ when $n_{\ell j} = 2$ and $\boldsymbol{\mu}_{T_\ell^{\bar{d}}} = (0,0,0,0,0)$ when $n_{\ell j} = 5$. The variance-covariance matrix $\mathbf{\Sigma}_{T_\ell^d}$ is a $m_{\ell i} \times m_{\ell i}$ matrix with diagonal elements equal to 1 and correlation coefficients equal to ρ and $\mathbf{\Sigma}_{T_\ell^{\bar{d}}}$ is a $n_{\ell j} \times n_{\ell j}$ matrix with diagonal elements equal to 1 and correlation coefficients equal to ρ

2. $T_\ell^d \sim LogNormal(\mu_{T_\ell^d}, \mathbf{\Sigma}_{T_\ell^d})$ and $T_\ell^{\bar{d}} \sim LogNormal(\mu_{T_\ell^{\bar{d}}}, \mathbf{\Sigma}_{T_\ell^{\bar{d}}})$, with the same settings on $\mu_{T_\ell^d}$, $\mathbf{\Sigma}_{T_\ell^d}$, $\mu_{T_\ell^{\bar{d}}}$, $\mathbf{\Sigma}_{T_\ell^{\bar{d}}}$, $m_{\ell i}$, $n_{\ell j}$ and ρ.

We let p, the informative cluster size correlation, be 0.3, 0.4 and 0.5. Note that when $p \neq 0.5$, the cluster size is different between the two groups. Under each setting, we let ρ, the within-cluster correlation, be 0.2, 0.5, 0.9 and $I/2$, the number of clusters in each group, be 25, 50 and 100.

B.3 Simulation Settings for Section 4.2

Let I_1 and I_0 denote the number of clusters in the diseased group and the nondiseased group. We let the two groups have the same number of clusters, so that $I_1 = I_0 = I/2$. The clusters in the diseased group have a cluster size $m_i = 3$ with probability p and a cluster size $m_i = 6$ with probability $1-p$, where as the clusters in the nondiseased group have a cluster size $n_j = 2$ with probability $1-p$ and a cluster size $n_j = 5$ with probability p. For a simplified ROC regression model, we simulate clustered ROC data such that , for the diseased group, $T \sim N(\boldsymbol{\mu}_X, \mathbf{\Sigma}_1)$, where $\boldsymbol{\mu}_X = (\mu_{D,X}, \mu_{D,X}, \mu_{\bar{D},X})$ when $m_i = 3$ and $\boldsymbol{\mu}_X = (\mu_{D,X}, \mu_{D,X}, \mu_{D,X}, \mu_{D,X}, \mu_{D,X}, \mu_{\bar{D},X})$ when $m_i = 6$. For the nondiseased group, $T \sim N(\boldsymbol{\mu}_{\bar{D},X}, \mathbf{\Sigma}_2)$, where $\boldsymbol{\mu}_{\bar{D},X} = (\mu_{D,X}, \mu_{\bar{D},X}, \mu_{D,X}, \mu_{\bar{D},X})$ when $n_j = 2$ and $\boldsymbol{\mu}_Y = (\mu_{\bar{D},X}, \mu_{\bar{D},X}, \mu_{\bar{D},X}, \mu_{\bar{D},X}, \mu_{\bar{D},X})$ when $n_j = 5$. The variance-covariance

matrix $\mathbf{\Sigma}_1$ is a $m_i \times m_i$ matrix with first $m_i - 1$ diagonal elements equal to σ_1, the last one diagonal elements equal to σ_0 and correlation coefficients equal to ρ and $\mathbf{\Sigma}_2$ is a $n_j \times n_j$ matrix with diagonal elements equal to σ_0 and correlation coefficients equal to ρ.

B.3.1 Simulation Settings for Section 4.2.1

For the simulated clustered ROC data associated with covariate x_1, we employ the proposed WCR indirect methods as well as the traditional indirect regression method. We assume a simple regression model with covariate $X = x_1$, so that $\mu_{D,x_1} = \beta_0 + \beta_1 + \beta_2 x_1 + \beta_3 x_1$ and $\mu_{\bar{D},x_1} = \beta_0 + \beta_2 x_1$. To simplify the model, we let $\beta_0 = \beta_1 = \beta_2 = 0$ and $\beta_3 = 0.3$. Thus the ROC curve associated with covariate $X = x_1$ is

$$ROC_{x_1}(u) = S_\epsilon(\frac{\sigma(0)}{\sigma(1)} S_\epsilon^{-1}(u) - \frac{\beta_3 x_1}{\sigma(1)}). \tag{2.1}$$

We generate random variable x_1 following Uniform (0,10). to estimate the ROC curve model parameter $\hat{\beta}_3$ and $\hat{\beta}_3/\hat{\sigma}_1$, we fit a simple regression model using least square method if the diseased and nondiseased groups have equal variance. We fit a simple regression model using weighted least square iF the diseased and nondiseased groups have unequal variances. We let $x_1 = 2, 5, 9$ to estimate the AUCs, $\widehat{AUC}_{x_1=2}$, $\widehat{AUC}_{x_1=5}$ and $\widehat{AUC}_{x_1=9}$. The variance of the parameter estimator $\hat{\beta}_3$, $\hat{var}(\hat{\beta}_3)$, is estimated by the least square method or the weighted least square method. The variances of other estimators $\widehat{var}(\hat{\beta}_3/\hat{\sigma}_1)$ $\widehat{var}(\widehat{AUC})_{x_1=2}$, $\widehat{var}(\widehat{AUC})_{x_1=5}$ and $\widehat{var}(\widehat{AUC})_{x_1=9}$ are estimated by the bootstrap method. We obtain the parameter estimators $\hat{\beta}_3$ and $\hat{\beta}_3/\hat{\sigma}_1$, the AUC estimators, $\widehat{AUC}_{x_1=2}$, $\widehat{AUC}_{x_1=5}$ and $\widehat{AUC}_{x_1=9}$, and the corresponding 95% confidence intervals from both methods.

B.3.2 Simulation Settings for Section 4.2.2

For the simulated clustered ROC data associated with continuous covariate x_1, The proposed WCR direct methods are used as well as traditional indirect regression method. We set the pairing margin

$\delta = \infty$ so that all the pairs can be included in the model

$$ROC_{x_D, x_{\bar{D}}}(u) = \Phi\{\alpha_0 + \alpha_1 \Phi^{-1}(u) + \beta_1 x_D + \beta_2 (x_D - x_{\bar{D}})\}. \tag{2.2}$$

The resulting AUC is given by,

$$AUC_{x_D, x_{\bar{D}}}(u) = \Phi^{-1}\{\beta_0 + \beta_1 x_D + \beta_2 (x_D - x_{\bar{D}})\}. \tag{2.3}$$

We also generate clustered ROC data with a categorical covariate $x_1 = 1, 2, 3, 4$ and 5. We create all the pairs within each level and fit the models to estimate the ROC curves and the AUC by

$$ROC_{x_D, x_{\bar{D}}}(u) = \Phi\{\alpha_0 + \alpha_1 \Phi^{-1}(u) + \beta_1 x_D\}, \tag{2.4}$$

and

$$AUC_{x_D, x_{\bar{D}}}(u) = \Phi^{-1}\{\beta_0 + \beta_1 x_D\}. \tag{2.5}$$

The parameter estimator $\hat{\beta}_1$ and the AUC estimator when $x_1 = 1$, $\widehat{AUC}_{x_1=1}$ are obtained.

Appendix C: R Packages

1. **library(MASS)**: The library is used to generate multivariate normal random variables and multivariate lognormal random variables. The command, **mvrnorm()**, is used to generate multivariate normal random variables in the simulation studies, including the simulation studies to estimate the AUC for one ROC curve in Section 2.2, the AUC difference for two ROC curves in Section 3.2 and the regression coefficients and the AUC for covariate adjusted ROC curves in Section 4.2.

2. **library(ggplot)**: The library is used to generate graphs. The command, **ggplot()**, is used to obtain the graphs for simulation results to compare the coverage percentage and confidence interval length under difference settings for simulation studies. The figures are in Sections 2.2, 3.2 and 4.2.

3. **library(lattice)**: The library is used to generate graphs. The command, **histogram()**, is used to show the distribution of the ratings used in our examples. The figures are in Appendix A.

The descriptions of the libraries and functions above are from R-CRAN.

Bibliography

Alonzo, T. A. and M. S. Pepe (2002). Distribution free ROC analysis using binary regression techniques. *Biostatistics 3*, 421–432.

Bamber, D. (1975). The area above the ordinal dominance graph and the area below the receive operating characteristic graph. *Journal of Mathematical Psychology 12*, 387–415.

Bandos, A. I., H. E. Rockette, and D. Gur (2005). A permutation test sensitive to differences in areas for comparing ROC curves from a paired design. *Statistics in Medicine 24*, 2873–2893.

Braun, T. M. and T. A. Alonzo (2008). A modified sign test for comparing paired ROC curves. *Biostatistics 9*, 364–372.

Cai, T. and C. S. Moskowitz (2004). Semi-parametric estimation of the binormal ROC curve for a continuous diagnostic test. *Biostatistics 5*(4), 573–586.

Cai, T. and M. S. Pepe (2002). Semiparametric receiver operating characteristic analysis to evaluate biomarkers for disease. *Journal of the American statistical Association 97*(460), 1099–1107.

Datta, S. and G. A. Satten (2005). Rank-sum tests for clustered data. *Journal of the American Statistical Association 100*(471), 908–915.

DeLong, E. R., D. M. DeLong, and D. L. Clarke-Pearson (1988). Comparing the areas under two or more correlated receiver operating characteristic curves: A nonparametric approach. *Journal of Biometrics 44*, 837–845.

Dodd, L. E. (2001). Regression methods for areas and partial areas under the ROC curve. *Ph.D. Thesis, University of Washington, Seattle, WA 1*, 1.

Dorfman, D. D. and E. A. Jr. (1969). Maximum-likelihood estimation of parameters of signal-detection theory and determination of confidence intervals rating-method data. *Journal of Mathematical Psychology 6*(3), 487 – 496.

Faraggi, D. and B. Reiser (2002). Estimation of the area under the ROC curve. *Statistics in medicine 21*(20), 3093–3106.

Follmann, D., M. Proschan, and E. Leifer (2003). Multiple outputation: inference for complex clustered data by averaging analyses from independent data. *Biometrics 59*(2), 420–429.

Goddard, M. J. and I. Hinberg (1990). Receiver operator characteristic (ROC) curves and non-normal data: An empirical study. *Statistics in Medicine 9*, 325–337.

Hanley, J. and B. McNeil (1982). The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology 143*, 29–36.

Hillis, S. L. and C. E. Metz (2012). An analytic expression for the binormal partial area under the ROC curve. *Academic Radiology 19*(12), 1491 – 1498.

Hoeffding, W. (1948). A class of statistics with asymptotically normal distribution. *The Annals of Mathematical Statistics 19*(3), 293–325.

Hoffman, E. B., P. K. Sen, and C. R. Weinberg (2001). Within-cluster resampling. *Biometrika 88*(4), 1121–1134.

Hsieh, F. and B. W. Turnbull (1996). Non- & semi- parametric estimation of the receiver operating characteristics (ROC) curve. *Annals of Statistics 24*, 25–40.

Jiang, C. E. M. and R. M. Nishikawa (1996). A receiver operating characteristic partial area index for highly sensitive diagnostic tests. *Radiology 201:3*, 745–750.

Jiang, L. H. (2005). Bayesian hierarchical modelling of glaucomatous visual field data. *unpublished doctoral dissertation, University of California Los Angeles, Dept. of Biostatistics*.

Li, G., R. Tiwari, and M. Wells (1999). Semiparametric inference for a quantile comparison function with applications to receiver operating characteristic curves. *Biometrika 86*, 487–502.

Li, G. and K. Zhou (2008). A unified approach to nonparametric comparison of receiver operating characteristic curves for longitudinal and clustered data. *Journal of the American Statistical Association 103*(482), 705–713.

Liang, K.-Y. and S. L. Zeger (1986). Longitudinal data analysis using generalized linear models. *Biometrika 73*(1), 13–22.

Lloyd, C. J. (1998). Using smoothed receiver operating characteristic curves to summarize and compare diagnostic systems. *J. Amer. Statist. Assoc. 93*, 1356–1364.

Lloyd, C. J. and Z. Yong (1999). Kernel estimators of the ROC curve are better than empirical. *Statistics Probability Letters 44*, 221 – 228.

Metz, C. E. (1978). Basic principles of ROC analysis. In *Seminars in nuclear medicine*, Volume 8, pp. 283–298.

Metz, C. E., B. A. Herman, J.-H. Shen, et al. (1998). Maximum likelihood estimation of receiver operating characteristic(ROC) curves from continuously-distributed data. *Statistics in medicine 17*(9), 1033–1053.

Obuchowski, N. A. (1997). Nonparametric analysis of clustered ROC curve data. *Biometrics 53*(2), pp. 567–578.

Pepe, M. S. (1997). A regression modelling framework for receiver operating characteristic curves in medical diagnostic testing. *Biometrika 84*(3), 595–608.

Pepe, M. S. (1998). Three approaches to regression analysis of receiver operating characteristic curves for continuous test results. *Biometrics*, 124–135.

Pepe, M. S. (2000). An interpretation for the ROC curve and inference using glm procedures. *Biometrics 56*, 352–359.

Qin, J. and B. Zhang (1997). A goodness-of-fit test for logistic regression models based on case-control data. *Biometrika 84*(3), 609–618.

Qin, J. and B. Zhang (2003). Using logistic regression procedures for estimating receiver operating characteristic curves. *Biometrika 90*(3), 585–596.

Rosner, B., R. J. Glynn, and M.-L. Lee (2003). Incorporation of clustering effects for the wilcoxon rank sum test: A large-sample approach. *Biometrics 59*(4), 1089–1098.

Shapiro, D. E. (1999). The interpretation of diagnostic tests. *Statistical Methods in Medical Research 8*(2), 113–134.

Tang, L. and X.-H. Zhou (2009). Semiparametric inferential procedures for comparing multivariate ROC curves with interaction terms. *Statistica Sinica 19*, 1203–1221.

Thompson, M. L. and W. Zucchini (1989). On the statistical analysis of ROC curves. *Statistics in Medicine 8*(10), 1277–1290.

Tosteson, A. N. A. and C. B. Begg (1988). A general regression methodology for ROC curve estimation. *Medical Decision Making 8*(3), 204–215.

Venkatraman, E. and C. B. Begg (1996). A distribution free procedure for comparing receiver operating characteristic curves from a paired experiment. *Biometrika 83*(4), 835–848.

Wan, S. and B. Zhang (2007). Smooth semiparametric receiver operating characteristic curves for continuous diagnostic tests. *Statistics in Medicine 26*, 2565–2586.

Wieand, S., M. H. Gail, B. R. James, and K. L. James (1989). A family of nonparametric statistics for comparing diagnostic markers with paired or unpaired data. *Biometrika 76*(3), 585–592.

Williamson, J. M., S. Datta, and G. A. Satten (2003). Marginal analyses of clustered data when cluster size is informative. *Biometrics 59*(1), 36–42.

Zeger, S. L. and K.-Y. Liang (1986). Longitudinal data analysis for discrete and continuous outcomes. *Biometrics 42*(1), pp. 121–130.

Zhou, X. H. and C. A. Gatsonis (1996). A simple method for comparing correlated ROC curves using incomplete data. *Statistics in Medicine 15*, 1687–1693.

Zhou, X.-H. and H. Lin (2008). Semi-parametric maximum likelihood estimates for ROC curves of continuous-scale tests. *Statistics in medicine 27*(25), 5271–5290.

Zhou, X. H., D. K. Mcclish, and N. A. Obuchowski (2002). *Statistical Methods in Diagnostic Medicine*. New York: John Wiley.

Zou, K. H. and W. J. Hall (2000). Two transformation models for estimating an ROC curve derived from continuous data. *Journal of Applied Statistics 27*(5), 621–631.

Zou, K. H., W. J. Hall, and D. E. Shapiro (1997). Smooth non-parametric receiver operating characteristic (ROC) curves for continuous diagnostic tests. *Statistics in Medicine 16*(19), 2143–2156.

Zou, K. H., C. M. Tempany, J. R. Fielding, and S. G. Silverman (1998). Original smooth receiver operating characteristic curve estimation from continuous data: Statistical methods for analyzing the predictive value of spiral ct of ureteral stones. *Academic Radiology 5*(10), 680 – 687.

Curriculum Vitae

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