Semiparametric inference of the Youden index and the optimal cut-off point under density ratio models

Meng YUAN, Pengfei LI*, and Changbao WU

Department of Statistics and Actuarial Science, University of Waterloo, Waterloo, Ontario, Canada

Key words and phrases: Density ratio model; empirical likelihood; optimal cut-off point; ROC curve; Youden index.

MSC 2010: Primary 62G05; secondary 62G20.

Abstract: The Youden index is a popular summary statistic for receiver operating characteristic curves. It gives the optimal cut-off point of a biomarker to distinguish the diseased and healthy individuals. In this article, we model the distributions of a biomarker for individuals in the healthy and diseased groups via a semiparametric density ratio model. Based on this model, we propose using the maximum empirical likelihood method to estimate the Youden index and the optimal cut-off point. We further establish the asymptotic normality of the proposed estimators and construct valid confidence intervals for the Youden index and the corresponding optimal cut-off point. The proposed method automatically covers both cases when there is no lower limit of detection (LLOD) and when there is a fixed and finite LLOD for the biomarker. Extensive simulation studies and a real data example are used to illustrate the effectiveness of the proposed method and its advantages over the existing methods. The Canadian Journal of Statistics 49: 965–986; 2021 © 2021 Statistical Society of Canada

1. INTRODUCTION

Receiver operating characteristic (ROC) curves are a widely used statistical tool in medical research to evaluate the discriminatory effectiveness of a biomarker for distinguishing diseased individuals from healthy ones. When the sampling distribution of the biomarker is continuous,
the ROC curve plots the proportion of true positive (sensitivity) versus proportion of false positive (one minus specificity) across all possible choices of threshold values, called cut-off points, of the biomarker. We refer to Zhou & Mcclish (2002), Pepe (2003), Krzanowski & Hand (2009), Zou et al. (2011), Chen et al. (2016), and references therein for comprehensive reviews and recent developments in ROC analysis.

The Youden index, first proposed by Youden (1950), is one of the popular summary statistics of the ROC curve. It is defined as the maximum of the sum of sensitivity and specificity minus one when the relative seriousness of a false positive and false negative are treated equally. The Youden index ranges from 0 to 1, with 1 indicating a complete separation of distributions of biomarkers in healthy and diseased populations and 0 indicating a complete overlap. It has the advantage of providing a criterion to choose the “optimal” cut-off point, which maximizes the sum of sensitivity and specificity minus one. See Fluss, Faraggi, & Reiser (2005) for more discussions on the advantages of the Youden index.

In medical research, larger values of a biomarker are generally associated with diseases. Therefore, an individual is classified as diseased when the biomarker of the individual is greater than a given cut-off point. Let \( F_0 \) and \( F_1 \) denote the cumulative distribution functions (CDFs) of the healthy population and the diseased population, respectively. The sensitivity and the specificity are respectively equal to \( 1 - F_1(x) \) and \( F_0(x) \) for the given cut-off point \( x \). Therefore, the Youden index can be equivalently expressed as

\[
J = \max_x \{F_0(x) - F_1(x)\} = F_0(c) - F_1(c),
\]

where \( c \) is the corresponding optimal cut-off point. In this article, we aim to develop efficient inferential procedures for \( J \) and \( c \).

In the literature, there are two types of methods, namely, the parametric methods and the nonparametric methods, for estimating the Youden index \( J \) and the corresponding optimal cut-off point \( c \). For parametric methods, the original biomarkers or the biomarkers after the Box–Cox transformation (Box & Cox, 1964) in the healthy and diseased groups are assumed to come from the same parametric distribution family (Fluss, Faraggi, & Reiser, 2005; Bantis, Nakas, & Reiser, 2019). Nonparametric methods employ techniques such as the empirical CDF (ECDF) method or the kernel method to obtain the estimators of \( F_0 \) and \( F_1 \), which are then used to obtain the point estimators of \( J \) and \( c \). More details about the ECDF-based and kernel-based methods, and their modified versions, can be found in Hsieh & Turnbull (1996), Zhou & Qin (2012), and Shan (2015). Recently, Bantis, Nakas, & Reiser (2019) employed hazard constrained natural spline (HCNS) as an alternative nonparametric approach to estimate \( J \) and \( c \). The delta and bootstrap methods (Schisterman & Perkins, 2007; Yin & Tian, 2014a; Bantis, Nakas, & Reiser, 2019) and the empirical likelihood (EL) methods (Wang, Tian, & Zhao, 2017b) are used to construct confidence intervals (CIs) for \( J \) and \( c \).

In applications, the measurement of a biomarker may have a fixed and finite lower limit of detection (LLOD). For instance, the quantitation of human immunodeficiency virus RNA in human plasma has an LLOD of 500 copies/ml with the Amplicor Monitor assay or has an LLOD of 50 copies/ml with the Ultrasensitive assay (Gulick et al., 2000). More examples of LLODs can be found in Ruopp et al. (2008), Bantis et al. (2017), and references therein. Ruopp et al. (2008) adapted the parametric method, the ECDF method, and the ROC-generalized linear model (ROC-GLM) method (Pepe, 2000; Alonzo & Pepe, 2002; Pepe, 2003) to obtain point estimates and construct CIs for \( J \) and \( c \) in those situations.

Generally speaking, the parametric likelihood-based estimators of \( (J, c) \) are quite efficient but may not be robust to model misspecifications (Fluss, Faraggi, & Reiser, 2005). Nonparametric methods are free from model assumptions on \( F_0 \) and \( F_1 \), but the resulting estimators of \( (J, c) \), especially the estimator of \( c \), may be inefficient. When there is no LLOD, Hsieh & Turnbull (1996)
showed that the convergence rates of the ECDF-based and the kernel-based estimators of $c$ are slower than $n^{-1/2}$, where $n$ is the total sample size.

In this article, we develop a semiparametric method that enables efficient estimation of both $J$ and $c$ without making risky parametric assumptions on $F_0$ and $F_1$. In medical research, the two populations under consideration usually share certain common characteristics (Qin & Zhang, 2003; Qin, 2017; Zhuang, Hu, & Chen, 2019). To incorporate the information from both samples, we suggest using the density ratio model (DRM), proposed by Anderson (1979) and Qin & Zhang (1997), to link $F_0$ and $F_1$ as

$$dF_1(x) = \exp\{\alpha + \beta^T q(x)\}dF_0(x) = \exp\{\theta^T Q(x)\}dF_0(x),$$

where $dF_k(x)$ denotes the density of $F_k(x)$ for $k = 0, 1$; the $q(x)$ is a prespecified, nontrivial function of dimension $p$; and $\theta^T = (\alpha, \beta^T)$ are unknown parameters. Note that $Q(x)^T = (1, q(x)^T)$. The unspecified baseline distribution $F_0$ makes DRM a semiparametric model. The DRM is quite flexible and includes many commonly used distribution families, such as normal, lognormal, and gamma distributions, as special cases.

In the literature, DRMs have been used as a platform to study inferential problems for the ROC curve and the area under the curve (AUC). Under the DRM, Qin & Zhang (2003) considered the estimation of the ROC curve and the AUC; Zhang (2006) proposed a Wald-type statistic to test whether the accuracy of a diagnostic test is acceptable in terms of the AUC; Wan & Zhang (2007) constructed a smoothed ROC curve estimator; and Jiang & Tu (2012) proposed two estimators for the AUC under censored data. Inspired by Qin & Zhou (2006), Wang & Zhang (2014) proposed an EL ratio-based CI for the AUC under DRMs. Later on, Wan & Zhang (2008) and Zhang & Zhang (2014) considered the inference problems for the difference of AUCs for two correlated ROC curves under a DRM. Other applications of DRMs include multiple-sample hypothesis-testing problems (Cai, Chen, & Zidek, 2017; Wang, Marriott, & Li, 2017a, 2018), quantile and quantile function estimation (Chen & Liu 2013), and dominance index estimation (Zhuang, Hu, & Chen, 2019). More detailed reviews can be found in Wang (2017). In general, the inference procedures based on DRMs are more efficient than the fully nonparametric procedures. To the best of our knowledge, the inference procedures for $(J, c)$ under a DRM have not been studied in the existing literature. This article fills that void.

Our contributions can be summarized as follows. We construct the maximum EL estimators (MELEs) of $(J, c)$ under a DRM based on the data with an LLOD, which automatically includes the case without an LLOD by setting the LLOD to be $-\infty$. We establish the $\sqrt{n}$ convergence rates and the asymptotic normality of the proposed estimators of $(J, c)$ for data without an LLOD or with a fixed and finite LLOD. Our results show that, when there is no LLOD, the proposed estimator of $c$ has a faster convergence rate than the existing nonparametric estimators, and the proposed estimator of $J$ is asymptotically more efficient than the existing nonparametric estimators. When there is a fixed and finite LLOD, the proposed method is the first semiparametric or nonparametric method with rigorous theoretical justifications. Simulation experiments show that the proposed estimators are more efficient than or comparable to nonparametric methods and are also comparable to parametric estimators under correctly specified distributions. In addition, the proposed estimator for the optimal cut-off point $c$ has clear advantages over existing ones for all scenarios considered in the simulation.

The rest of the article is organized as follows. In Section 2, we propose the MELEs of $J$ and $c$ under a DRM and study their asymptotic results. Confidence intervals of $J$ and $c$ are then constructed based on the asymptotic results. Simulation studies are presented in Section 3, and a real data application is given in Section 4. We conclude with some discussion and additional remarks in Section 5. All technical details are provided in the Appendix.
2. MAIN RESULTS
2.1. Point Estimation of J and c under the DRM

Denote \( \{x_{01}, \ldots, x_{0n_0}\} \) and \( \{x_{11}, \ldots, x_{1n_1}\} \) as two independent random samples coming from the healthy and diseased populations, respectively. Let \( f_0 \) and \( f_1 \) be the probability density functions of \( F_0 \) and \( F_1 \), respectively. Following the definition of Youden index in (1), the optimal cut-off point \( c \) satisfies \( f_0(c) = f_1(c) \), which together with (2) implies that

\[
\theta^T Q(c) = 0. \tag{3}
\]

The above equation serves as the basis for estimating \( c \).

In the following, we focus on cases where the biomarker has an LLOD, denoted as \( r \), and develop estimators for \( (J, c) \). Analysis of data without an LLOD amounts to setting \( r = -\infty \).

Let \( m_0 \) and \( m_1 \) be the numbers of observations above the LLOD \( r \) in the healthy and diseased groups, respectively. Let \( \zeta_0 = P(x_{01} \geq r) \) and \( \zeta_1 = P(x_{11} \geq r) \). Without loss of generality, we use \( \{t_1, \ldots, t_m\} = \{x_{kj}, j = 1, \ldots, m_k, k = 0, 1\} \) to denote the observations in the two samples, which are above the LLOD, where \( m = m_0 + m_1 \).

We now discuss the maximum EL procedure for estimating the unknown parameters and functions. By the EL principle (Owen, 2001) and under the DRM (2), the full likelihood can be written as

\[
L_n = \prod_{k=0}^{1} (1 - \zeta_k)^{n_k - m_k} \prod_{j=1}^{m} df_k(X_{kj}) = \prod_{k=0}^{1} (1 - \zeta_k)^{n_k - m_k} \prod_{i=1}^{m} p_i \prod_{i=m_0+1}^{m} \exp\{\theta^T Q(t_i)\},
\]

where \( p_i = df_0(t_i) \) for \( i = 1, \ldots, m \) and they satisfy the following constraints:

\[
p_i \geq 0, \quad 0 < \sum_{i=1}^{m} p_i = \zeta_0 \leq 1, \quad 0 < \sum_{i=1}^{m} p_i \exp\{\theta^T Q(t_i)\} = \zeta_1 \leq 1. \tag{4}
\]

The MELEs of \( (\theta, \zeta_0, \zeta_1, p_1, \ldots, p_m) \), denoted as \( (\hat{\theta}, \hat{\zeta}_0, \hat{\zeta}_1, \hat{p}_1, \ldots, \hat{p}_m) \), are defined as the maximizer of \( L_n \) subject to the constraints in Equation (4). Cai & Chen (2018) show that

\[
\hat{\zeta}_k = m_k/n_k, \quad k = 0, 1
\]

and the \( \hat{\theta} \) maximizes the following dual profile empirical log-likelihood function

\[
\ell_n(\theta) = \sum_{i=m_0+1}^{m} \{\theta^T Q(t_i)\} - \sum_{i=1}^{m} \log \left[ 1 + \rho \exp\{\theta^T Q(t_i)\} \right].
\]

where \( \rho = n_1/n_0 \). That is, \( \hat{\theta} = \arg \max_{\theta} \ell_n(\theta) \). The MELEs of \( p_i \)'s are given by

\[
\hat{p}_i = n_0^{-1} \left[ 1 + \rho \exp\{\hat{\theta}^T Q(t_i)\} \right]^{-1}, \quad i = 1, \ldots, m.
\]
It follows that, for any \( x \geq r \), the MELEs of \( F_0 \) and \( F_1 \) are given by

\[
\hat{F}_0(x) = (1 - \hat{\psi}_0) + \frac{1}{n} \sum_{i=1}^{n} \frac{\exp\{\hat{\theta}^T Q(t_i)\}}{1 + \rho \exp\{\hat{\theta}^T Q(t_i)\}} I(r \leq t_i \leq x),
\]

\[
\hat{F}_1(x) = (1 - \hat{\psi}_1) + \frac{1}{n} \sum_{i=1}^{n} \frac{\exp\{\hat{\theta}^T Q(t_i)\}}{1 + \rho \exp\{\hat{\theta}^T Q(t_i)\}} I(r \leq t_i \leq x),
\]

where \( I(\cdot) \) is the indicator function.

With the MELE \( \hat{\theta} \) and Equation (3), the MELE of the optimal cut-off point \( c \), denoted as \( \hat{c} \), can be obtained as the solution to the equation

\[
\hat{\theta}^T Q(x) = 0. \tag{5}
\]

If multiple solutions exist for (5) in \([\min t_i, \max t_i]\), we choose the one that attains the maximum of \( \hat{F}_0(x) - \hat{F}_1(x) \) as \( \hat{c} \). If a solution to (5) does not exist in the range \([\min t_i, \max t_i]\), we set \( \hat{c} \) to be

\[
\hat{c} = \arg \max_{x \in \{t_i : i = 1, \ldots, m\}} \{\hat{F}_0(x) - \hat{F}_1(x)\}. \tag{6}
\]

The MELE \( \hat{J} \) of \( J \) is then given by \( \hat{J} = \hat{F}_0(\hat{c}) - \hat{F}_1(\hat{c}) \).

We conclude this section with a brief discussion on \( \hat{c} \). According to the proof of Lemma 1 in the Appendix, as \( n \to \infty \), with probability approaching 1, Equation (5) has a solution in the neighbourhood of \( c_0 \). However, when \( n \) is not large, and \( c_0 \) is close to the LLOD, Equation (5) may not have a solution in the range \([\min t_i, \max t_i]\). In such situations, Equation (6) ensures that \( \hat{c} \) is well defined.

### 2.2. Asymptotic Properties

In this section, we study the asymptotic properties of the MELEs \((\hat{J}, \hat{c})\) described in Section 2.1. We first introduce some further notation. Let \( \theta_0 \) be the true value of \( \theta \) and \( \omega(x) = \exp\{\theta_0^T Q(x)\} \). For \( t \geq r \), define

\[
A_0(t) = \int_r^t \frac{\omega(x)}{1 + \rho \omega(x)} dF_0(x),
\]

\[
A_1(t) = \int_r^t \frac{\omega(x)q(x)}{1 + \rho \omega(x)} dF_0(x),
\]

\[
A_2(t) = \int_r^t \frac{\omega(x)q(x)q^T(x)}{1 + \rho \omega(x)} dF_0(x).
\]

Furthermore, let \( A_0 = A_0(\infty), A_1 = A_1(\infty), A_2 = A_2(\infty) \), and

\[
A = \begin{pmatrix} A_0 & A_1^T \\ A_1 & A_2 \end{pmatrix}, \quad S = \frac{\rho}{1 + \rho} A, \quad V = S - \rho \begin{pmatrix} A_0 \\ A_1 \end{pmatrix} (A_0, A_1^T).
\]

Define \( q(x) = dq(x)/dx \).
Theorem 1. Let \((J_0, c_0)\) be the true value of \((J, c)\). Suppose the regularity conditions in the Appendix are satisfied and \(c_0 > r\). As the total sample size \(n = n_0 + n_1\) goes to infinity, we have

(a) \(\sqrt{n}(\hat{c} - c_0) \to N(0, \sigma_c^2)\) in distribution, where

\[
\sigma_c^2 = \frac{Q(c_0)^T S^{-1} V S^{-1} Q(c_0)}{\{\beta_0^T q(c_0)\}^2},
\]

and \(\beta_0\) is the true value of \(\beta\);

(b) \(\sqrt{n}(\hat{J} - J_0) \to N(0, \sigma_J^2)\) in distribution, where

\[
\sigma_J^2 = (\rho + 1)\{F_0(c_0) - F_0^2(c_0)\} + \frac{\rho + 1}{\rho}\{F_1(c_0) - F_1^2(c_0)\}

- \frac{(\rho + 1)^3}{\rho}\left\{A_0(c_0) - \left(\begin{array}{c} A_0(c_0) \\ A_1(c_0) \end{array}\right)^T A^{-1} \left(\begin{array}{c} A_0(c_0) \\ A_1(c_0) \end{array}\right)\right\}.
\]

We provide some comments on the results of Theorem 1. Let \((\hat{J}_E, \hat{c}_E)\) and \((\hat{J}_K, \hat{c}_K)\) be the ECDF-based and kernel-based estimators of \((J, c)\), respectively. First, the estimators \(\hat{J}\) and \(\hat{c}\) both reach the convergence rates of the parametric likelihood-based estimators. When there is no LLOD or \(r = -\infty\), the convergence rate of \(\hat{c}\) is faster than \(\hat{c}_E\) and \(\hat{c}_K\). Second, when there is no LLOD or \(r = -\infty\), Hsieh & Turnbull (1996) showed that

\[
nE\{(\hat{J}_E - J_0)^2\} = \sigma_N^2 + O(n^{-1/3}), \quad nE\{(\hat{J}_K - J_0)^2\} = \sigma_N^2 - \gamma n^{-1/3} \{1 + o(1)\}
\]

for some \(\gamma > 0\), where

\[
\sigma_N^2 = (\rho + 1)\{F_0(c_0) - F_0^2(c_0)\} + \frac{\rho + 1}{\rho}\{F_1(c_0) - F_1^2(c_0)\}.
\]

Here, the two bandwidths for the kernel method have the order \(n^{-\nu}\) for some \(0 < \nu < 1/3\). According to Theorem 1 in Qin & Zhang (1997), \(\sigma_N^2 - \sigma_J^2 \geq 0\). Hence, when \(n\) is large, the asymptotic mean square error of \(\hat{J}\) is smaller than those of \(\hat{J}_E\) and \(\hat{J}_K\).

2.3. Confidence Intervals on \(J\) and \(c\) under the DRM

Replacing \((\theta_0, J_0, c_0, F_0)\) in \(\sigma_J^2\) and \(\sigma_c^2\) with their respective estimators \((\hat{\theta}, \hat{J}, \hat{c}, \hat{F}_0)\), we obtain the estimators \((\hat{\sigma}_J^2, \hat{\sigma}_c^2)\) for \((\sigma_J^2, \sigma_c^2)\). It can be shown that \(\hat{\sigma}_J^2\) and \(\hat{\sigma}_c^2\) are both consistent.

Theorem 2. Under the conditions of Theorem 1, we have

\(\hat{\sigma}_J^2 \to \sigma_J^2\) and \(\hat{\sigma}_c^2 \to \sigma_c^2\)

in probability as \(n \to \infty\).

Because of the asymptotic normality of \(\hat{c}\) presented in Theorem 1 and the consistency of \(\hat{\sigma}_c^2\), the quantity \(\sqrt{n}(\hat{c} - c_0)/\hat{\sigma}_c\) is asymptotically pivotal, which leads to the following Wald-type CI for \(c\) at level \(1 - a\):

\[
I_c = \left[\hat{c} - z_{1-a/2} \hat{\sigma}_c / \sqrt{n}, \hat{c} + z_{1-a/2} \hat{\sigma}_c / \sqrt{n}\right],
\]

where \(z_{1-a/2}\) is the 100\((1 - a/2)\)th quantile of the standard normal distribution.
We can similarly construct a Wald-type CI for $J$. However, the Wald-type CI for $J$ based on $\hat{J}$ directly is not range preserving. When $J$ is close to the boundary 0 or 1, the lower or upper bound of the Wald-type CIs could lie outside the range $[0, 1]$. Naturally, we consider a logit transformation on $\hat{J}$ when constructing the CI for $J$. The resulting CI for $J$ is range-preserving.

Furthermore, our simulation experience indicates that the logit transformation on $\hat{J}$ leads to a CI for $J$ with better coverage accuracy, especially when $J_0$ is close to 0 or 1. More specifically, using the results in Theorems 1 and 2, it can be shown that

$$\sqrt{n}(\logit(\hat{J}) - \logit(J_0)) \rightarrow N\left(0, \frac{\sigma_J^2}{J_0(1-J_0)^2}\right)$$

in distribution as $n \rightarrow \infty$, where $\logit(x) = \log\{x/(1-x)\}$ for $0 < x < 1$. Hence $\sqrt{n}(1-\hat{J})(\logit(\hat{J}) - \logit(J_0))/\hat{\sigma}_J$ is also asymptotically pivotal. This suggests the following CI for $J$:

$$I_J = \left[\text{expit}\left\{\logit(\hat{J}) - \frac{z_{1-a/2}\hat{\sigma}_J}{\sqrt{n}(1-\hat{J})}\right\}, \text{expit}\left\{\logit(\hat{J}) + \frac{z_{1-a/2}\hat{\sigma}_J}{\sqrt{n}(1-\hat{J})}\right\}\right],$$

where $\text{expit}(x) = \exp(x)/(1 + \exp(x))$.

3. SIMULATION STUDIES

3.1. Candidate Methods

In this section, we report results from simulation studies to compare the proposed point estimators and CIs of $J$ and $c$ with the following candidate methods.

- The Box–Cox method in Bantis, Nakas, & Reiser (2019), where the corresponding point estimators and CIs of $J$ and $c$ are denoted as $\hat{J}_B$, $\hat{c}_B$, $I_{JB}$, and $I_{cB}$, respectively.
- The ROC-GLM method in Ruopp et al. (2008), where the corresponding point estimators and CIs of $J$ and $c$ are denoted as $\hat{J}_G$, $\hat{c}_G$, $I_{cG}$, and $I_{cG}$, respectively.
- The ECDF-based method, where the corresponding point estimators and CIs of $J$ and $c$ are denoted as $\hat{J}_E$, $\hat{c}_E$, $I_{JE}$, and $I_{cE}$, respectively.
- The kernel-based method in Bantis, Nakas, & Reiser (2019), where the corresponding point estimators and CIs of $J$ and $c$ are denoted as $\hat{J}_K$, $\hat{c}_K$, $I_{JK}$, and $I_{cK}$, respectively.
- The HCNS method in Bantis, Nakas, & Reiser (2019), where the corresponding point estimators and CIs of $J$ and $c$ are denoted as $\hat{J}_H$, $\hat{c}_H$, $I_{JH}$, and $I_{cH}$, respectively.

For all the above candidate methods, except for $I_{JB}$, which is obtained via the delta method, the CIs are constructed using the nonparametric bootstrap percentile method. Further details on these methods are provided in the Supplementary Material document.

When there is no LLOD, we compare the proposed method and all the candidate methods listed above. When there is a fixed and finite LLOD, to the best of our knowledge, the kernel-based method and the HCNS method have not been explored in the literature, and hence, we do not include these two methods in the comparisons.

3.2. Simulation Setup

We conduct simulation studies under the following two distributional settings from Fluss, Faraggi, & Reiser (2005):

DOI: 10.1002/cjs.11600
Here, $\text{Gamma}(\kappa, \eta)$ denotes the gamma distribution with shape parameter $\kappa$ and rate parameter $\eta$, and $\text{LN}(\mu, \sigma^2)$ denotes the lognormal distribution with mean $\mu$ and variance $\sigma^2$, both with respect to the log scale. The proposed estimators are calculated under the correctly specified $q(x)$. For the setting with gamma distributions, we have $q(x) = x$, and for the setting with lognormal distributions, we have $q(x) = (\log x, \log^2 x)^T$.

For each setting, we choose four values of $\eta$ or $\mu$ such that the corresponding Youden indices equal 0.2, 0.4, 0.6, and 0.8. The details are given in Table 1 of the Supplementary Material. For the LLOD, we consider three values: $-\infty$, 15% quantile of $F_0$, and 30% quantile of $F_0$. The exact values of LLOD for the latter two cases are given in Table 2 of the Supplementary Material. Note that, when the LLOD equals $-\infty$, there is no LLOD. For each simulation scenario, we consider five sample size combinations: $(n_0, n_1) = (50, 50), (100, 100), (200, 200), (150, 50)$, and $(50, 150)$, and results are based on 1,000 repeated simulation runs.

The simulation results from different simulation scenarios demonstrate similar patterns. To save space, we only report the simulation results under the setting with gamma distribution, without LLOD and with LLOD equal to the 15% quantile of $F_0$. Other simulation results are provided in the Supplementary Material.

### 3.3. Comparison for Point Estimators

We first examine the point estimators of $(J, c)$. The performance of a point estimator is evaluated through relative bias (RB) in percentage and mean squared error (MSE) computed as

$$RB = \frac{1}{B} \sum_{b=1}^{B} \frac{a^{(b)} - a_0}{a_0} \times 100, \quad MSE = \frac{1}{B} \sum_{b=1}^{B} (a^{(b)} - a_0)^2,$$

where $a_0$ is the true value of the parameter of interest, $a^{(b)}$ is the estimator of $a_0$ from the $b$th simulation run, and $B = 1,000$ is the number of simulation runs. The simulation results are presented in Tables 1–4.

When there is no LLOD, major observations from Tables 1 and 2 can be summarized as follows. For estimating the Youden index $J$, the ECDF-based estimator $J_E$ has the largest RBs and MSEs in almost all the cases. We also notice that, when $J = 0.2$, the RBs of $J_B$, $J_G$, and $J_H$ have RBs greater than 5%, which may not be acceptable, especially when one of $n_0$ and $n_1$ is small. The estimators $J$, $J_B$, $J_G$, and $J_H$ have comparable performance in terms of MSE, which are uniformly better than $J_E$ and $J_H$. When sample sizes are small, the kernel-based estimator $J_K$ has slightly smaller MSE than $J$; when the sample size increases, the proposed estimator $\hat{J}$ becomes more efficient in terms of MSE. This is in line with our discussion after Theorem 1.

For estimating the optimal cut-off point $c$, the proposed estimator $\hat{c}$ outperforms other estimators significantly for the majority of cases. The parametric estimator $\hat{c}_B$ is the most competitive. It has larger MSEs than $\hat{c}$ when $J = 0.2, 0.4$, and 0.6 and has slightly smaller MSEs than $\hat{c}$ when $J = 0.8$. Among the other four estimators, the estimator $\hat{c}_E$ has the worst performance, and $\hat{c}_G$ shows the best performance in most cases. The performances of $\hat{c}_K$ and $\hat{c}_H$ are mixed. There is no obvious trend that one has dominating performance over others.

When the LLOD equals 15% quantile of $F_0$, Tables 3 and 4 show that the general trend for comparing the proposed method with the Box–Cox method, ROC-GLM method, and ECDF-based method are similar to the case when there is no LLOD. It is worth mentioning that, as the LLOD increases, the MSEs of all estimators increase due to the loss of information.
under censoring. The estimation of the optimal cut-off point $c$ is more sensitive to the increase of LLOD, especially when $J$ is small.

### 3.4. Comparison for Confidence Intervals

We now examine the behaviour of 95% CIs of $J$ and $c$. The performance of a CI is evaluated by the coverage probability (CP) in percentage and the average length (AL), computed as

$$CP = \frac{1}{B} \sum_{b=1}^{B} \mathbb{I}(a_0 \in I^{(b)}) \times 100, \quad AL = \frac{1}{B} \sum_{b=1}^{B} |I^{(b)}|,$$

where $I^{(b)}$ is the CI of the interested quantity computed from the $b$th simulation run, and $|\cdot|$ is the length of the CI. The simulation results are presented in Tables 5–8.
We first summarize the findings on the CIs for the Youden index $J$. The CPs of $I_{JE}$ have low coverage probabilities and are not acceptable regardless of the value of LLODs. The proposed CI and the CI based on the Box–Cox method, $I_J$ and $I_{JB}$, respectively, have the most stable and comparable performance in almost all cases. The ROC-GLM-based CI, $I_{JG}$, performs quite well in general but has undercoverage issues in some cases. When there is no LLOD, the two confidence intervals $I_{JK}$ and $I_{JH}$ have similar issues as $I_{JG}$ with undercoverage problems.

We next discuss the findings on the CIs for the optimal cut-off point $c$. When there is no LLOD, the proposed CI $I_{cJ}$ has the most stable performance, and its CPs are reasonably close to 95% in almost all scenarios. The CPs of $I_{cE}$ fluctuate around the nominal level of 95%, while undercoverage problems are associated with the other four CIs $I_{cB}$, $I_{cG}$, $I_{cK}$, and $I_{cH}$. When there is a fixed and finite LLOD, the ALs of all CIs increase. The proposed CI $I_{c}$ and the ECDF-based CI $I_{cE}$ tend to have an issue with overcoverage, while the CI based on the Box–Cox method has severe undercoverage problem, and the ROC-GLM based CI $I_{cG}$ also
**Table 3**: RB (%) and MSE (×100) for point estimators of $J$ when the LLOD equals 15% quantile of $F_0$.

| $J$ $(n_0, n_1)$ | (50, 50) | (100, 100) | (200, 200) | (50, 150) | (150, 50) |
|-----------------|---------|---------|---------|--------|--------|
|                 | RB   | MSE   | RB   | MSE   | RB   | MSE   | RB   | MSE   | RB   | MSE   |
| 0.2             | $\hat{J}$ | 5.92 | 0.61 | 2.49 | 0.31 | 1.11 | 0.14 | 4.62 | 0.40 | 2.85 | 0.42 |
|                 | $\hat{J}_B$ | 9.59 | 0.64 | 4.75 | 0.32 | 2.85 | 0.15 | 7.38 | 0.41 | 5.85 | 0.43 |
|                 | $\hat{J}_G$ | 7.58 | 0.69 | 2.67 | 0.36 | -0.34 | 0.17 | 5.99 | 0.46 | 3.50 | 0.50 |
|                 | $\hat{J}_E$ | 40.17 | 1.29 | 26.63 | 0.64 | 17.72 | 0.30 | 33.04 | 0.86 | 32.69 | 0.89 |
| 0.4             | $\hat{J}$ | 2.69 | 0.57 | 1.10 | 0.30 | 0.51 | 0.13 | 1.88 | 0.36 | 1.31 | 0.40 |
|                 | $\hat{J}_B$ | 4.92 | 0.59 | 2.59 | 0.29 | 1.75 | 0.14 | 3.59 | 0.36 | 3.12 | 0.41 |
|                 | $\hat{J}_G$ | 1.50 | 0.61 | -0.21 | 0.32 | -1.20 | 0.15 | 0.68 | 0.39 | -0.01 | 0.46 |
|                 | $\hat{J}_E$ | 16.42 | 1.06 | 10.62 | 0.53 | 6.78 | 0.24 | 13.36 | 0.68 | 12.57 | 0.74 |
| 0.6             | $\hat{J}$ | 1.74 | 0.46 | 0.6 | 0.24 | 0.29 | 0.11 | 1.04 | 0.27 | 0.85 | 0.34 |
|                 | $\hat{J}_B$ | 3.17 | 0.44 | 1.70 | 0.22 | 1.19 | 0.11 | 2.16 | 0.27 | 2.09 | 0.32 |
|                 | $\hat{J}_G$ | 0.11 | 0.47 | -0.64 | 0.26 | -1.04 | 0.12 | -0.56 | 0.29 | -0.35 | 0.38 |
|                 | $\hat{J}_E$ | 8.89 | 0.76 | 5.38 | 0.37 | 3.71 | 0.19 | 7.14 | 0.48 | 6.73 | 0.56 |
| 0.8             | $\hat{J}$ | 1.10 | 0.26 | 0.40 | 0.14 | 0.16 | 0.06 | 0.58 | 0.14 | 0.63 | 0.21 |
|                 | $\hat{J}_B$ | 1.58 | 0.22 | 0.80 | 0.11 | 0.56 | 0.05 | 1.01 | 0.12 | 1.02 | 0.17 |
|                 | $\hat{J}_G$ | -0.60 | 0.30 | -0.65 | 0.16 | -0.80 | 0.08 | -0.94 | 0.17 | -0.39 | 0.24 |
|                 | $\hat{J}_E$ | 4.51 | 0.39 | 2.86 | 0.20 | 1.94 | 0.10 | 3.73 | 0.24 | 3.53 | 0.30 |

**Table 4**: RB (%) and MSE (×100) for point estimators of $c$ when the LLOD equals 15% quantile of $F_0$.

| $J$ $(n_0, n_1)$ | (50, 50) | (100, 100) | (200, 200) | (50, 150) | (150, 50) |
|-----------------|---------|---------|---------|--------|--------|
|                 | RB   | MSE   | RB   | MSE   | RB   | MSE   | RB   | MSE   | RB   | MSE   |
| 0.2             | $\hat{c}$ | -1.58 | 60.04 | -0.86 | 24.25 | -0.44 | 10.84 | -1.53 | 38.67 | -0.60 | 66.67 |
|                 | $\hat{c}_B$ | 1.04 | 148.39 | 0.49 | 51.29 | -0.30 | 24.87 | 0.29 | 66.35 | -0.07 | 67.79 |
|                 | $\hat{c}_G$ | 6.30 | 168.58 | 8.65 | 81.29 | 8.51 | 48.7 | 6.72 | 90.4 | 9.00 | 102.15 |
|                 | $\hat{c}_E$ | -0.65 | 257.51 | 0.49 | 170.8 | -0.76 | 116.8 | -0.79 | 202.38 | 1.89 | 223.79 |
| 0.4             | $\hat{c}$ | -0.59 | 23.70 | -0.24 | 11.48 | -0.04 | 5.58 | -0.67 | 15.51 | -0.15 | 15.28 |
|                 | $\hat{c}_B$ | -0.82 | 47.68 | -0.54 | 24.65 | -0.57 | 12.19 | -1.06 | 31.41 | -0.33 | 29.38 |
|                 | $\hat{c}_G$ | 2.35 | 75.60 | 5.21 | 47.69 | 5.98 | 30.66 | 4.04 | 51.81 | 6.34 | 54.94 |
|                 | $\hat{c}_E$ | -2.89 | 160.26 | -0.23 | 126.83 | -0.45 | 75.26 | -2.66 | 150.21 | 1.51 | 156.93 |
| 0.6             | $\hat{c}$ | -0.39 | 32.90 | -0.22 | 16.35 | -0.01 | 7.71 | -0.63 | 23.81 | 0.01 | 19.68 |
|                 | $\hat{c}_B$ | -1.05 | 48.30 | -0.81 | 23.92 | -0.64 | 11.46 | -1.48 | 31.25 | -0.27 | 26.75 |
|                 | $\hat{c}_G$ | 0.18 | 91.92 | 2.33 | 51.66 | 3.77 | 29.23 | 2.04 | 52.36 | 3.34 | 50.15 |
|                 | $\hat{c}_E$ | -2.29 | 161.37 | -0.67 | 118.08 | 0.16 | 74.77 | -2.40 | 147.73 | 1.22 | 146.35 |
| 0.8             | $\hat{c}$ | -0.45 | 72.29 | -0.34 | 36.11 | 0.02 | 17.60 | -0.87 | 53.45 | 0.17 | 41.41 |
|                 | $\hat{c}_B$ | -0.65 | 66.17 | -0.46 | 32.77 | -0.17 | 15.11 | -1.24 | 48.59 | 0.25 | 35.50 |
|                 | $\hat{c}_G$ | -3.53 | 193.47 | -0.26 | 92.54 | 1.59 | 52.64 | 0.28 | 91.43 | -0.43 | 99.37 |
|                 | $\hat{c}_E$ | -3.17 | 236.85 | -1.72 | 159.92 | -1.24 | 107.54 | -4.03 | 195.30 | 1.09 | 197.79 |
### Table 5: CP (%) and AL for CIs of \( J \) when there is no LLOD.

| \( J \) | \((n_0, n_1)\) | \((50, 50)\) | \((100, 100)\) | \((200, 200)\) | \((50, 150)\) | \((150, 50)\) |
|---|---|---|---|---|---|---|
| 0.2 | \( I_J \) | 94.1 | 0.32 | 94.9 | 0.22 | 96.4 | 0.15 | 93.6 | 0.25 | 94.7 | 0.26 |
|   | \( I_{JB} \) | 94.5 | 0.30 | 93.9 | 0.21 | 95.2 | 0.15 | 92.7 | 0.24 | 94.6 | 0.25 |
|   | \( I_{KG} \) | 92.6 | 0.29 | 93.7 | 0.21 | 94.7 | 0.15 | 91.9 | 0.23 | 93.7 | 0.25 |
|   | \( I_{JE} \) | 70.2 | 0.30 | 72.1 | 0.22 | 78.0 | 0.16 | 66.7 | 0.24 | 72.6 | 0.26 |
|   | \( I_{JK} \) | 93.6 | 0.30 | 93.7 | 0.23 | 94.7 | 0.16 | 92.3 | 0.25 | 93.7 | 0.26 |
|   | \( I_{JH} \) | 92.1 | 0.31 | 94.0 | 0.23 | 94.1 | 0.17 | 91.1 | 0.25 | 93.3 | 0.27 |
| 0.4 | \( I_J \) | 95.4 | 0.28 | 94.9 | 0.20 | 96.0 | 0.14 | 93.3 | 0.22 | 94.3 | 0.24 |
|   | \( I_{JB} \) | 95.1 | 0.28 | 94.2 | 0.20 | 95.3 | 0.14 | 93.1 | 0.22 | 94.2 | 0.24 |
|   | \( I_{KG} \) | 93.1 | 0.29 | 93.6 | 0.20 | 94.7 | 0.14 | 91.6 | 0.22 | 92.9 | 0.25 |
|   | \( I_{JE} \) | 79.2 | 0.30 | 80.5 | 0.22 | 83.5 | 0.16 | 75.1 | 0.23 | 80.4 | 0.26 |
|   | \( I_{JK} \) | 93.7 | 0.29 | 93.1 | 0.21 | 95.1 | 0.15 | 92.7 | 0.23 | 93.5 | 0.24 |
|   | \( I_{JH} \) | 93.7 | 0.31 | 95.0 | 0.22 | 94.7 | 0.16 | 93.3 | 0.23 | 96.5 | 0.28 |
| 0.6 | \( I_J \) | 95.6 | 0.25 | 94.3 | 0.18 | 95.0 | 0.13 | 94.2 | 0.19 | 94.0 | 0.22 |
|   | \( I_{JB} \) | 95.8 | 0.25 | 94.2 | 0.18 | 95.1 | 0.13 | 93.8 | 0.19 | 94.2 | 0.22 |
|   | \( I_{KG} \) | 93.3 | 0.26 | 93.5 | 0.18 | 94.8 | 0.13 | 92.5 | 0.19 | 92.6 | 0.23 |
|   | \( I_{JE} \) | 79.4 | 0.26 | 80.7 | 0.19 | 85.3 | 0.14 | 75.7 | 0.20 | 81.8 | 0.23 |
|   | \( I_{JK} \) | 94.4 | 0.24 | 94.1 | 0.17 | 95.4 | 0.13 | 92.4 | 0.19 | 93.5 | 0.21 |
|   | \( I_{JH} \) | 94.0 | 0.30 | 95.3 | 0.21 | 95.3 | 0.15 | 92.6 | 0.21 | 95.8 | 0.27 |
| 0.8 | \( I_J \) | 95.1 | 0.20 | 94.0 | 0.14 | 95.0 | 0.10 | 95.1 | 0.14 | 95.9 | 0.18 |
|   | \( I_{JB} \) | 96.0 | 0.18 | 94.1 | 0.13 | 95.3 | 0.09 | 94.1 | 0.13 | 95.2 | 0.16 |
|   | \( I_{KG} \) | 92.7 | 0.20 | 94.0 | 0.14 | 95.2 | 0.10 | 93.3 | 0.14 | 92.2 | 0.18 |
|   | \( I_{JE} \) | 81.6 | 0.19 | 85.5 | 0.14 | 85.9 | 0.10 | 76.1 | 0.14 | 83.5 | 0.17 |
|   | \( I_{JK} \) | 95.0 | 0.17 | 91.8 | 0.13 | 91.0 | 0.09 | 93.6 | 0.13 | 92.3 | 0.15 |
|   | \( I_{JH} \) | 86.9 | 0.23 | 95.8 | 0.17 | 95.5 | 0.12 | 92.8 | 0.17 | 92.2 | 0.22 |

has the same issue for some cases. When \( J = 0.4, 0.6, \) and \( 0.8 \), the proposed CI \( I_c \) becomes quite stable in almost all cases. The performance of \( I_{cB} \) improves as \( J \) increases. The CPs of \( I_{cG} \) are reasonably close to the nominal level. However, \( I_{cG} \) has longer ALs compared to \( I_c \).

### 4. REAL DATA ANALYSIS

In this section, we illustrate the performance of the proposed method by analyzing a dataset on Duchenne Muscular Dystrophy (DMD). DMD is a genetic disorder characterized by progressive muscle degeneration and weakness. A particular gene on the X chromosome, when mutated, leads to DMD. This disease is transmitted from a mother to her children genetically. Affected male offspring usually develop the disease and die at a young age, while the mutated gene does not affect the health of female offspring. Therefore, detection of potential affected females is of great interest.
Percy, Andrews, & Thompson (1982) pointed out that carriers of DMD tend to exhibit high levels of certain biomarkers even though they do not show any symptoms. Andrews & Herzberg (2012) collected the complete data of four biomarkers, namely, creatine kinase (CK), hemopexin (H), lactate dehydrogenase (LD), and pyruvate kinase (PK), from the blood serum samples of a healthy group of people ($n_0 = 127$) and a group of carriers ($n_1 = 67$). Our goal is to choose the most appropriate biomarker to distinguish healthy individuals from diseased ones.

We choose $q(x) = x$ in the proposed method for each biomarker, which is equivalent to assuming a logistic regression model for an individual’s disease status and the biomarker (Qin & Zhang 1997). Table 9 presents Qin & Zhang (1997)’s test statistics along with the $P$-values for the goodness of fit of the DRM in (2) with $q(x) = x$. It shows that, for each biomarker, the data do not provide evidence to reject the DRM in (2) with $q(x) = x$.

Table 10 provides the point estimates and the CIs (in parentheses) from the proposed method and all the competitive methods listed in Section 3. As we can see, for all biomarkers, the point

### Table 6: CP (%) and AL for CIs of $c$ when there is no LLOD.

| $J$  | $(n_0, n_1)$ | (50, 50) | (100, 100) | (200, 200) | (50, 150) | (150, 50) |
|------|--------------|----------|-------------|------------|-----------|-----------|
|      | CP           | AL       | CP          | AL         | CP        | AL        | CP        | AL        |
| 0.2  | $I_c$        | 94.1     | 1.31        | 94.1       | 0.94      | 95.2      | 0.67      | 94.2      | 1.11      | 94.8      | 1.05      |
|      | $I_{cB}$     | 92.8     | 7.26        | 93.9       | 2.64      | 93.8      | 1.77      | 93.7      | 3.25      | 92.6      | 3.25      |
|      | $I_{cG}$     | 94.0     | 4.50        | 94.7       | 3.02      | 94.3      | 2.07      | 93.7      | 3.43      | 94.8      | 3.47      |
|      | $I_{cE}$     | 97.0     | 5.36        | 96.5       | 4.65      | 96.8      | 3.89      | 95.6      | 4.83      | 97.2      | 5.05      |
|      | $I_{cK}$     | 95.6     | 7.02        | 94.3       | 5.70      | 95.0      | 3.89      | 95.2      | 6.68      | 92.6      | 6.36      |
|      | $I_{cH}$     | 97.2     | 5.98        | 97.9       | 4.79      | 95.8      | 3.67      | 96.4      | 4.59      | 95.4      | 5.80      |
| 0.4  | $I_c$        | 93.9     | 1.63        | 94.5       | 1.16      | 95.6      | 0.82      | 93.3      | 1.40      | 94.5      | 1.27      |
|      | $I_{cB}$     | 92.0     | 2.38        | 92.0       | 1.72      | 92.5      | 1.23      | 92.5      | 1.98      | 92.1      | 1.83      |
|      | $I_{cG}$     | 91.5     | 3.13        | 94.0       | 2.30      | 93.4      | 1.63      | 92.2      | 2.36      | 93.4      | 2.31      |
|      | $I_{cE}$     | 95.1     | 4.52        | 96.6       | 3.80      | 95.0      | 3.18      | 94.2      | 4.02      | 96.8      | 4.32      |
|      | $I_{cK}$     | 93.9     | 4.23        | 93.2       | 2.91      | 93.4      | 2.19      | 94.3      | 3.55      | 92.5      | 3.13      |
|      | $I_{cH}$     | 97.0     | 4.87        | 95.6       | 3.83      | 94.6      | 2.92      | 94.4      | 3.97      | 97.1      | 4.58      |
| 0.6  | $I_c$        | 93.2     | 2.13        | 94.4       | 1.52      | 95.0      | 1.08      | 93.4      | 1.85      | 94.0      | 1.63      |
|      | $I_{cB}$     | 91.5     | 2.36        | 92.1       | 1.70      | 92.2      | 1.21      | 91.4      | 1.99      | 92.3      | 1.76      |
|      | $I_{cG}$     | 90.2     | 3.57        | 90.8       | 2.59      | 92.4      | 1.86      | 90.9      | 2.57      | 91.1      | 2.44      |
|      | $I_{cE}$     | 94.5     | 4.43        | 95.7       | 3.76      | 97.0      | 3.05      | 92.2      | 3.96      | 95.9      | 4.21      |
|      | $I_{cK}$     | 92.7     | 3.60        | 90.9       | 2.73      | 90.0      | 2.04      | 92.7      | 3.31      | 87.8      | 2.65      |
|      | $I_{cH}$     | 96.7     | 4.80        | 96.6       | 3.76      | 96.4      | 2.78      | 94.7      | 3.80      | 97.6      | 4.50      |
| 0.8  | $I_c$        | 92.9     | 3.25        | 94.3       | 2.31      | 95.0      | 1.65      | 93.8      | 2.78      | 93.7      | 2.46      |
|      | $I_{cB}$     | 91.9     | 2.87        | 93.3       | 2.03      | 94.5      | 1.44      | 90.6      | 2.49      | 93.8      | 2.14      |
|      | $I_{cG}$     | 87.8     | 5.18        | 91.5       | 3.81      | 90.0      | 2.71      | 92.0      | 3.65      | 86.6      | 3.27      |
|      | $I_{cE}$     | 88.8     | 4.93        | 93.7       | 4.28      | 93.9      | 3.55      | 84.5      | 4.42      | 94.5      | 4.78      |
|      | $I_{cK}$     | 91.3     | 4.34        | 90.9       | 3.29      | 89.7      | 2.49      | 92.1      | 4.06      | 88.8      | 3.16      |
|      | $I_{cH}$     | 95.6     | 4.74        | 97.3       | 3.99      | 94.8      | 2.91      | 93.6      | 3.97      | 98.7      | 4.74      |
Table 7: CP (%) and AL for CIs of $J$ when the LLOD equals 15% quantile of $F_0$.

| $J$ | $(n_0, n_1)$ | (50, 50) | (100, 100) | (200, 200) | (50, 150) | (150, 50) |
|-----|--------------|----------|----------|----------|----------|----------|
|     |              | CP       | AL       | CP       | AL       | CP       | AL       | CP       | AL       | CP       | AL       |
| 0.2 | $I_j$        | 93.4     | 0.31     | 94.2     | 0.21     | 96.0     | 0.15     | 93.8     | 0.25     | 94.3     | 0.25     |
|     | $I_{JB}$     | 94.3     | 0.30     | 93.9     | 0.21     | 95.2     | 0.15     | 92.6     | 0.24     | 94.5     | 0.25     |
|     | $I_{KG}$     | 93.2     | 0.31     | 94.0     | 0.23     | 94.7     | 0.16     | 92.9     | 0.25     | 93.2     | 0.26     |
|     | $I_{JE}$     | 64.8     | 0.28     | 68.2     | 0.21     | 73.4     | 0.15     | 61.4     | 0.23     | 65.0     | 0.24     |
| 0.4 | $I_j$        | 95.3     | 0.28     | 94.9     | 0.20     | 95.8     | 0.15     | 93.7     | 0.22     | 94.5     | 0.24     |
|     | $I_{JB}$     | 95.4     | 0.28     | 94.0     | 0.20     | 95.4     | 0.14     | 93.3     | 0.22     | 94.6     | 0.24     |
|     | $I_{KG}$     | 94.6     | 0.30     | 94.8     | 0.22     | 95.2     | 0.15     | 92.7     | 0.24     | 93.3     | 0.26     |
|     | $I_{JE}$     | 77.4     | 0.28     | 78.5     | 0.21     | 81.7     | 0.15     | 73.8     | 0.22     | 78.1     | 0.25     |
| 0.6 | $I_j$        | 95.7     | 0.26     | 94.6     | 0.18     | 94.7     | 0.13     | 94.0     | 0.19     | 94.2     | 0.22     |
|     | $I_{JB}$     | 95.7     | 0.25     | 94.2     | 0.18     | 94.7     | 0.13     | 93.8     | 0.19     | 94.2     | 0.22     |
|     | $I_{KG}$     | 94.3     | 0.27     | 93.9     | 0.19     | 94.5     | 0.14     | 92.9     | 0.20     | 93.4     | 0.23     |
|     | $I_{JE}$     | 77.6     | 0.25     | 79.3     | 0.19     | 82.8     | 0.14     | 74.3     | 0.19     | 80.3     | 0.22     |
| 0.8 | $I_j$        | 95.5     | 0.20     | 94.2     | 0.14     | 95.3     | 0.10     | 94.9     | 0.14     | 95.7     | 0.18     |
|     | $I_{JB}$     | 96.2     | 0.18     | 94.8     | 0.13     | 94.6     | 0.09     | 94.6     | 0.13     | 95.2     | 0.16     |
|     | $I_{KG}$     | 93.7     | 0.21     | 93.5     | 0.15     | 95.4     | 0.11     | 94.3     | 0.15     | 93.8     | 0.19     |
|     | $I_{JE}$     | 80.2     | 0.18     | 85.3     | 0.14     | 86.4     | 0.10     | 75.1     | 0.14     | 83.1     | 0.17     |

Table 8: CP (%) and AL for CIs of $c$ when the LLOD equals 15% quantile of $F_0$.

| $J$ | $(n_0, n_1)$ | (50, 50) | (100, 100) | (200, 200) | (50, 150) | (150, 50) |
|-----|--------------|----------|----------|----------|----------|----------|
|     |              | CP       | AL       | CP       | AL       | CP       | AL       | CP       | AL       | CP       | AL       |
| 0.2 | $I_c$        | 97.5     | 5.97     | 97.5     | 1.95     | 96.5     | 1.26     | 96.9     | 2.73     | 96.8     | 4.02     |
|     | $I_{cB}$     | 83.6     | 5.06     | 83.7     | 2.10     | 81.8     | 1.43     | 77.4     | 2.35     | 84.8     | 2.74     |
|     | $I_{cG}$     | 95.3     | 4.83     | 93.1     | 3.27     | 89.5     | 2.23     | 91.1     | 3.80     | 91.9     | 3.77     |
|     | $I_{cE}$     | 96.6     | 5.07     | 95.4     | 4.41     | 96.9     | 3.75     | 94.6     | 4.55     | 96.4     | 4.82     |
| 0.4 | $I_c$        | 95.3     | 1.87     | 95.0     | 1.32     | 95.7     | 0.93     | 94.0     | 1.53     | 95.5     | 1.52     |
|     | $I_{cB}$     | 86.8     | 2.19     | 87.9     | 1.58     | 87.8     | 1.12     | 83.5     | 1.58     | 91.3     | 1.84     |
|     | $I_{cG}$     | 94.3     | 3.20     | 92.7     | 2.36     | 87.3     | 1.68     | 91.2     | 2.48     | 92.0     | 2.41     |
|     | $I_{cE}$     | 95.1     | 4.43     | 95.9     | 3.74     | 95.3     | 3.14     | 93.6     | 3.93     | 97.3     | 4.27     |
| 0.6 | $I_c$        | 93.4     | 2.17     | 94.3     | 1.55     | 95.3     | 1.10     | 93.5     | 1.85     | 94.3     | 1.70     |
|     | $I_{cB}$     | 91.0     | 2.39     | 91.3     | 1.71     | 92.1     | 1.22     | 87.8     | 1.81     | 93.0     | 1.91     |
|     | $I_{cG}$     | 94.0     | 3.59     | 94.2     | 2.62     | 92.3     | 1.88     | 93.7     | 2.65     | 93.6     | 2.51     |
|     | $I_{cE}$     | 94.4     | 4.40     | 95.5     | 3.72     | 96.5     | 3.04     | 91.6     | 3.94     | 95.9     | 4.17     |
| 0.8 | $I_c$        | 92.9     | 3.24     | 94.4     | 2.31     | 94.9     | 1.65     | 93.2     | 2.78     | 93.7     | 2.48     |
|     | $I_{cB}$     | 92.8     | 2.99     | 94.9     | 2.14     | 94.7     | 1.52     | 91.1     | 2.51     | 94.2     | 2.27     |
|     | $I_{cG}$     | 92.5     | 5.28     | 95.0     | 3.79     | 94.8     | 2.71     | 94.2     | 3.74     | 92.8     | 3.39     |
|     | $I_{cE}$     | 88.5     | 4.90     | 93.5     | 4.26     | 94.3     | 3.54     | 84.7     | 4.39     | 94.3     | 4.76     |
TABLE 9: Qin & Zhang (1997)’s test statistics and their $P$-values when $q(x) = x$.

| Biomarker | CK | LD | PH | H |
|-----------|----|----|----|---|
| Test statistic | 0.138 | 0.247 | 0.226 | 0.222 |
| $P$-value | 0.912 | 0.291 | 0.507 | 0.676 |

TABLE 10: Estimation of the Youden index and the optimal cut-off point with the DMD dataset.

| | CK | LD | PK | H |
|---|----|----|----|---|
| $\hat{J}$ | 0.59 (0.49, 0.67) | 0.55 (0.46, 0.64) | 0.49 (0.40, 0.57) | 0.36 (0.28, 0.46) |
| $\hat{J}_B$ | 0.62 (0.51, 0.70) | 0.56 (0.46, 0.66) | 0.48 (0.37, 0.58) | 0.37 (0.26, 0.48) |
| $\hat{J}_G$ | 0.60 (0.50, 0.71) | 0.57 (0.47, 0.68) | 0.48 (0.38, 0.61) | 0.39 (0.29, 0.50) |
| $\hat{J}_E$ | 0.61 (0.52, 0.73) | 0.58 (0.50, 0.72) | 0.51 (0.42, 0.65) | 0.42 (0.34, 0.57) |
| $\hat{J}_K$ | 0.59 (0.51, 0.67) | 0.55 (0.45, 0.66) | 0.47 (0.37, 0.58) | 0.37 (0.25, 0.49) |
| $\hat{J}_H$ | 0.61 (0.52, 0.80) | 0.57 (0.46, 0.70) | 0.48 (0.35, 0.62) | 0.40 (0.31, 0.56) |

estimates of the Youden index are similar for all methods: They differ only in the second digit. For the CIs of the Youden index, the methods with $\hat{J}$, $\hat{J}_B$, $\hat{J}_G$, and $\hat{J}_K$ have similar performances for all biomarkers; the CIs with $\hat{J}_E$ and $\hat{J}_H$ tend to be wider than the other four methods. For the optimal cut-off point, the point estimates have substantial differences, especially for the biomarker LD, compared with the estimates of the Youden index. For all biomarkers, the proposed method has the shortest CIs, while the ECDF-based and HCNS methods tend to have the widest CIs. The performances of other three CIs are mixed: the CI based on the Box–Cox method has a shorter length for biomarkers CK and LD, while the CIs based on ROC-GLM and kernel methods have shorter length for biomarkers PK and H. Furthermore, we find that the biomarker CK gives the largest estimated Youden index, which is around 0.6. Therefore, the biomarker CK performs the best among these four biomarkers to distinguish the diseased individuals and the healthy ones. The estimated optimal cut-off point for the biomarker CK using the proposed method is 61.13, with the 95% CI being (55.64, 66.62).

5. CONCLUDING REMARKS

In this article, we propose linking the distributions of the biomarkers in the diseased and healthy groups via the DRM (2). Based on this model, we obtain the MELEs of the Youden index and the corresponding optimal cut-off point. We further establish the asymptotic normality of the estimators, which enables us to construct valid CIs for the Youden index and the corresponding optimal cut-off point. The proposed method covers cases without an LLOD and cases with a fixed and finite LLOD. Simulation studies and a real data application demonstrate the advantages of the proposed method over existing methods.

DOI: 10.1002/cjs.11600

The Canadian Journal of Statistics / La revue canadienne de statistique
One problem arising from the simulation studies is that the proposed confidence interval \( I_c \) for the optimal cut-off point could have under/overcoverage issues under certain scenarios, especially when there is a fixed and finite LLOD and one of the sample sizes is small. A possible alternative approach is to consider the EL ratio-based CI for \( c \). Another problem is related to the real data application where there are multiple biomarkers. Yin & Tian (2014b) studied the optimal linear combination of multiple biomarkers based on the Youden index. We can first use the DRM to link multiple biomarkers, construct a derived optimal linear combination of the biomarkers, and find the optimal cut-off point based on the derived biomarker. Both research problems are currently under investigation.

We conclude the article with some discussion on the choice of \( q(x) \). To use the proposed method, we need to specify \( q(x) \) in advance. If the practitioners believe that a logistic regression model is adequate to describe the relationship between the individual’s disease status and the biomarker, then they can use the DRM (2) with \( q(x) = x \). If the practitioners believe that gamma distributions or lognormal distributions provide a good fit to the biomarkers in the healthy and diseased groups, then they can use the semiparametric DRM (2) with \( q(x) = (x, \log x)^T \) or \((\log x, \log^2 x)^T\) instead of a parametric model to achieve robustness of inferences. The DRM (2) with a particular choice of \( q(x) \) can be further checked by the goodness-of-fit test discussed in Qin & Zhang (1997). We have implemented the proposed method along with Qin & Zhang (1997)’s test for some commonly used \( q(x) \) in an R package \texttt{YoudenDRM}. It is available upon request. However, if the practitioners do not have any prior belief or information on the distributions of the biomarkers in the healthy and diseased groups, then a nonparametric method such as the kernel-based method and the HCNS method may be preferable.

APPENDIX

Regularity Conditions

The asymptotic properties of \( (\hat{J}, \hat{c}) \) rely on the following regularity conditions.

C1. For any \( \epsilon > 0 \), \( J_\epsilon = \sup_{|x-c_0| \geq \epsilon} \{ F_0(x) - F_1(x) \} < J_0 \).

C2. The first and second derivatives of \( F_0(x) \) and \( F_1(x) \) are continuous in the neighbourhood of \( c_0 \), with \( F_0'(c_0) - F_1'(c_0) = 0 \) and \( F_0''(c_0) - F_1''(c_0) < 0 \).

C3. The total sample size \( n = n_0 + n_1 \rightarrow \infty \) and \( p = n_1/n_0 \) remains a constant.

C4. The two CDFs \( F_0 \) and \( F_1 \) satisfy the DRM (2) with a true parameter value \( \theta_0 \) and \( \int_r^\infty \exp\{\theta^T Q(x)\} dF_0 < \infty \) in a neighbourhood of \( \theta_0 \), and \( \int_r^\infty Q(x)Q(x)^T dF_0(x) \) is positive definite.

Condition C1 is from Hsieh & Turnbull (1996), which ensures \( c_0 \) is unique. Condition C2 comes from the definitions of the Youden index and its corresponding optimal cut-off point. Conditions C3 and C4 guarantee that the asymptotic results in Cai & Chen (2018) can be applied.

Proof of Theorem 1.

Some preliminary results are provided and serve as preparation for the proof of Theorem 1. We first introduce some further notation. Let

\[
H(x) = F_0(x) - F_1(x), \quad \hat{H}(x) = \hat{F}_0(x) - \hat{F}_1(x).
\]

Then, \( J_0 = H(c_0) \) and \( \hat{J} = \hat{H}(\hat{c}) \). Furthermore, let

\[
\Delta_{n0} = \sup_{x \geq r} |\hat{F}_0(x) - F_0(x)|, \quad \Delta_{n1} = \sup_{x \geq r} |\hat{F}_1(x) - F_0(x)|, \quad \Delta_n = \sup_{x \geq r} |\hat{H}(x)|.
\]
Following the proof of Lemma 3 in Cai & Chen (2018), we have $\Delta_{n0} = O_p(n^{-1/2})$ and $\Delta_{n1} = O_p(n^{-1/2})$. Hence, $\Delta_n = O_p(n^{-1/2})$.

We can establish the consistency of $\hat{c}$ and argue that, when the probability goes to 1, the estimator $\hat{c}$ is the solution to $\hat{\theta}^T Q(x) = 0$.

**Lemma 1.** Assume Conditions C1–C4 are satisfied. Then, as $n \to \infty$, we have

\[
\hat{c} \to c_0 \quad \text{in probability} \quad \text{(A1)}
\]

and

\[
P\left(\hat{\theta}^T Q(\hat{c}) = 0\right) \to 1. \quad \text{(A2)}
\]

**Proof.** For (A1) to hold, it is sufficient to show that, for any $0 < \varepsilon < c_0 - r$,

\[
\lim_{n \to \infty} P(\hat{c} > c_0 + \varepsilon) = 0, \quad \text{(A3)}
\]

\[
\lim_{n \to \infty} P(\hat{c} < c_0 - \varepsilon) = 0. \quad \text{(A4)}
\]

We focus on proving (A3). The other part in (A4) can be similarly proven. We choose $\varepsilon^* < \varepsilon$ such that

(a) $H(x) \geq \frac{J_0 + J_{\varepsilon}}{2}$, for $x \in [c_0 - \varepsilon^*, c_0 + \varepsilon]$;

(b) $\theta_0^T Q(c_0 - \varepsilon^*) < 0$ and $\theta_0^T Q(c_0 + \varepsilon^*) > 0$.

Using Conditions C1 and C2, the existence of such $\varepsilon^*$ is obvious. We further define a subset of the sample space as $A_{n,e} = A_{n1,e} \cap A_{n2,e} \cap A_{n3,e}$, where

\[
A_{n1,e} = \left\{ \hat{\theta}^T Q(c_0 - \varepsilon^*) < \frac{1}{2} \theta_0^T Q(c_0 - \varepsilon^*) \right\},
\]

\[
A_{n2,e} = \left\{ \hat{\theta}^T Q(c_0 + \varepsilon^*) > \frac{1}{2} \theta_0^T Q(c_0 + \varepsilon^*) \right\},
\]

\[
A_{n3,e} = \left\{ \inf_{x \in [c_0 - \varepsilon^*, c_0 + \varepsilon^*]} \hat{H}(x) \geq \frac{J_0 + 3J_{\varepsilon}}{4} \right\}.
\]

The two subsets $A_{n1,e}$ and $A_{n2,e}$ together ensure that there exists a solution $\hat{c}^*$ to $\hat{\theta}^T Q(x) = 0$ in $[c_0 - \varepsilon^*, c_0 + \varepsilon^*]$, and $A_{n3,e}$ implies that $\hat{H}(\hat{c}^*)$ is very close to $J_0$.

With the choice of $\varepsilon^*$, the consistency of $\hat{\theta}$ (Cai & Chen 2018), and the fact that $\Delta_n = O_p(n^{-1/2})$, it can be shown that

\[
\lim_{n \to \infty} P(A_{n1,e}) = \lim_{n \to \infty} P(A_{n2,e}) = \lim_{n \to \infty} P(A_{n3,e}) = 1. \quad \text{(A5)}
\]

The details are sketched as follows. By the choice of $\varepsilon^*$,

\[
P(A_{n1,e}) = P\left(\hat{\theta}^T Q(c_0 - \varepsilon^*) - \theta_0^T Q(c_0 - \varepsilon^*) < \frac{1}{2} \theta_0^T Q(c_0 - \varepsilon^*)\right)
\]

\[
\geq P\left(\left|\hat{\theta}^T Q(c_0 - \varepsilon^*) - \theta_0^T Q(c_0 - \varepsilon^*)\right| < \frac{1}{2} \theta_0^T Q(c_0 - \varepsilon^*)\right).
\]
Then, by the consistency of \( \hat{\theta} \) (Cai & Chen 2018), we have \( \lim_{n \to \infty} P(A_{n1, \epsilon}) = 1 \). Similarly, we also have \( \lim_{n \to \infty} P(A_{n2, \epsilon}) = 1 \). As for the third term \( A_{n3, \epsilon} \), again by the choice of \( \epsilon_* \), when \( x \in [c_0 - \epsilon_*, c_0 + \epsilon_*] \), we have

\[
\hat{H}(x) = (\hat{H}(x) - H(x) + H(x)) \geq -\Delta_n + \frac{J_0 + J_\epsilon}{2}.
\]

Therefore,

\[
P(A_{n3, \epsilon}) \geq P\left(-\Delta_n + \frac{J_0 + J_\epsilon}{2} \geq \frac{J_0 + 3J_\epsilon}{4}\right) = P\left(\Delta_n \leq \frac{J_0 - J_\epsilon}{4}\right).
\]

As \( \Delta_n = O_p(n^{-\frac{1}{2}}) \), we have \( \lim_{n \to \infty} P(A_{n3, \epsilon}) = 1 \).

We are now ready to prove \( (A3) \). Note that

\[
P(\hat{c} > c_0 + \epsilon) \leq P\left(H(\hat{c}) \leq J_\epsilon\right) \leq P\left(\hat{H}(\hat{c}) \leq J_\epsilon + \Delta_n\right)
\]

\[
\leq P\left(\{\hat{H}(\hat{c}) \leq J_\epsilon + \Delta_n\} \cap A_{n, \epsilon}\right) + P(A_{n, \epsilon}^c).
\]

By the definition of \( A_{n, \epsilon} \), if \( \{\hat{H}(\hat{c}) \leq J_\epsilon + \Delta_n\} \) and \( A_{n, \epsilon} \) both occur, we have

\[
J_\epsilon + \Delta_n \geq \hat{H}(\hat{c}) \geq \hat{H}(\hat{c}^*) \geq \inf_{x \in [c_0 - \epsilon_*, c_0 + \epsilon_*]} \hat{H}(x) \geq \frac{J_0 + 3J_\epsilon}{4},
\]

which implies \( \Delta_n \geq (J_0 - J_\epsilon)/4 \). Hence,

\[
P(\hat{c} > c_0 + \epsilon) \leq P\left(\Delta_n \geq \frac{J_0 - J_\epsilon}{4}\right) + P(A_{n, \epsilon}^c) \to 0,
\]

where the last step follows from \( (A5) \) and \( \Delta_n = O_p(n^{-\frac{1}{2}}) \). This finishes the proof of \( (A3) \) and the consistency of \( \hat{c} \) stated in \( (A1) \).

For \( (A2) \), we note that

\[
A_{n1, \epsilon} \cap A_{n2, \epsilon} \subset \left\{ \hat{\theta}^T Q(\hat{c}) = 0 \right\},
\]

which, together with \( (A5) \), implies that

\[
\lim_{n \to \infty} P\left(\hat{\theta}^T Q(\hat{c}) = 0\right) = 1.
\]

This completes the proof of \( (A2) \).

---

**Proof of Theorem 1.** We first consider Part (a). By \( (A2) \) of Lemma 1 and Slutsky’s theorem, we can derive the asymptotic normality of \( \hat{c} \) from \( \hat{\theta}^T Q(\hat{c}) = 0 \). Applying the first-order Taylor expansion on \( q(\hat{c}) \) at the point \( x = c_0 \) and using the consistency result of \( \hat{c} \) in \( (A1) \) of Lemma 1, we have

\[
0 = \hat{\alpha} + \hat{\beta}^T q(c_0) + \hat{\beta}^T q(c_0) (\hat{c} - c_0) + o_p(1) \cdot (\hat{c} - c_0).
\]

By Theorem 1 of Cai & Chen (2018), we have

\[
\sqrt{n}(\hat{\theta} - \theta_0) \to N(0, S^{-1} VS^{-1}) \quad (A6)
\]
in distribution as \( n \to \infty \). This, together with the fact \( \theta_0^T Q(c_0) = 0 \), implies that

\[
\sqrt{n}(\hat{c} - c_0) = -\frac{Q^T(c_0)}{\beta_0^T q(c_0)} \left\{ \sqrt{n}(\hat{\theta} - \theta_0) \right\} + o_p(1) \to N(0, \sigma_c^2)
\]

in distribution as \( n \to \infty \), where \( \sigma_c^2 \) is defined in (7).

We next consider Part (b). Recall that

\[
\hat{J} - J_0 = \{\hat{F}_0(\hat{c}) - \hat{F}_1(\hat{c})\} - \{F_0(c_0) - F_1(c_0)\}.
\]

Let

\[
M_{n0} = \hat{F}_0(c_0) - F_0(c_0), \quad M_{n1} = \hat{F}_1(c_0) - F_1(c_0),
\]

\[
e_{n0} = \{\hat{F}_0(\hat{c}) - \hat{F}_0(c)\} - \{F_0(\hat{c}) - F_0(c_0)\},
\]

\[
e_{n1} = \{\hat{F}_1(\hat{c}) - \hat{F}_1(c)\} - \{F_1(\hat{c}) - F_1(c_0)\},
\]

\[
e_{n2} = \{F_0(\hat{c}) - F_1(\hat{c})\} - \{F_0(c_0) - F_1(c_0)\}.
\]

It can be shown that

\[
\hat{J} - J_0 = M_{n0} - M_{n1} + e_{n0} + e_{n1} + e_{n2}. \tag{A7}
\]

One of the key technical arguments is to show that \( e_{n0}, e_{n1}, \) and \( e_{n2} \) are all of order \( o_p(n^{-1/2}) \).

By Lemma 4 of Cai & Chen (2018), we have for any \( b > 0 \),

\[
\sup_{x:|x-c_0|<bn^{-1/2}} |\{\hat{F}_0(x) - \hat{F}_0(c_0)\} - \{F_0(x) - F_0(c_0)\}| = O_p(n^{-3/4}(\log(n))^{1/2}) = o_p(n^{-1/2}). \tag{A8}
\]

The result in Part (a) implies that \( \hat{c} - c_0 = O_p(n^{-1/2}) \), which, together with (A8), leads to \( e_{n0} = o_p(n^{-1/2}) \). Similarly, we also have \( e_{n1} = o_p(n^{-1/2}) \). By the second-order Taylor expansion and Condition A2, we have \( e_{n2} = o_p(n^{-1/2}) \). It follows that

\[
\sqrt{n}(\hat{J} - J_0) = \sqrt{n}(M_{n0} - M_{n1}) + o_p(1). \tag{A9}
\]

Applying Theorem 2 of Cai & Chen (2018), we have

\[
\sqrt{n} \begin{pmatrix} M_{n0} \\ M_{n1} \end{pmatrix} = \sqrt{n} \begin{pmatrix} \hat{F}_0(c_0) - F_0(c_0) \\ \hat{F}_1(c_0) - F_1(c_0) \end{pmatrix} \to N \left( 0, \begin{pmatrix} \sigma_{00}^2 & \sigma_{01}^2 \\ \sigma_{01}^2 & \sigma_{11}^2 \end{pmatrix} \right) \tag{A10} \]

in distribution as \( n \to \infty \), where

\[
\sigma_{00}^2 = (1 + \rho)[F_0(c_0) - F_0^2(c_0)] - \rho(1 + \rho) \left\{ A_0(c_0) - \begin{pmatrix} A_0(c_0) \\ A_1(c_0) \end{pmatrix}^T A^{-1} \begin{pmatrix} A_0(c_0) \\ A_1(c_0) \end{pmatrix} \right\},
\]

\[
\sigma_{01}^2 = \frac{1}{2} \left\{ \frac{A_0}{A_1} \right\}^T A^{-1} \left\{ \frac{A_0}{A_1} \right\}.
\]

\[
\sigma_{11}^2 = \frac{1}{2} \left\{ \frac{A_0}{A_1} \right\}^T A^{-1} \left\{ \frac{A_0}{A_1} \right\}.
\]
\[ \sigma_{01}^2 = (1 + \rho) \left\{ A_0(c_0) - \begin{pmatrix} A_0(c_0) \\ A_1(c_0) \end{pmatrix}^T A^{-1} \begin{pmatrix} A_0(c_0) \\ A_1(c_0) \end{pmatrix} \right\}, \]

\[ \sigma_{11}^2 = \frac{1 + \rho}{\rho} \left\{ F_1(c_0) - F_2^2(c) \right\} - \frac{1 + \rho}{\rho} \left\{ A_0(c_0) - \begin{pmatrix} A_0(c_0) \\ A_1(c_0) \end{pmatrix}^T A^{-1} \begin{pmatrix} A_0(c_0) \\ A_1(c_0) \end{pmatrix} \right\}. \]

It immediately follows that, as \( n \to \infty \),

\[ \sqrt{n} \left( M_{n0} - M_{n1} \right) \to N(0, \sigma_j^2) \]

in distribution, where \( \sigma_j^2 \) is defined in (8). Recall that \( \sqrt{n}(\hat{J} - J_0) = \sqrt{n} \left( M_{n0} - M_{n1} \right) + o_p(1) \). By Slutsky’s theorem, we have

\[ \sqrt{n}(\hat{J} - J_0) \to N(0, \sigma_j^2) \]

in distribution as \( n \to \infty \). This completes the proof of the theorem. \( \blacksquare \)

ACKNOWLEDGEMENTS

The authors thank the Editor, the Associate Editor, and two reviewers for their constructive comments and suggestions, which led to major improvement of the article. This research was supported by grants from the Natural Sciences and Engineering Research Council of Canada.

BIBLIOGRAPHY

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

Anderson, J. A. (1979). Multivariate logistic compounds. *Biometrika*, 66, 17–26.

Andrews, D. F. & Herzberg, A. M. (2012). *Data: A Collection of Problems from Many Fields for the Student and Research Worker*. Springer, New York.

Bantis, L. E., Nakas, C. T., & Reiser, B. (2019). Construction of confidence intervals for the maximum of the Youden index and the corresponding cutoff point of a continuous biomarker. *Biometrical Journal*, 61, 138–156.

Bantis, L. E., Yan, Q., Tsimikas, J. V., & Feng, Z. (2017). Estimation of smooth ROC curves for biomarkers with limits of detection. *Statistics in Medicine*, 36, 3830–3843.

Box, G. E. P. & Cox, D. R. (1964). An analysis of transformations. *Journal of the Royal Statistical Society, Series B*, 26, 211–252.

Cai, S. & Chen, J. (2018). Empirical likelihood inference for multiple censored samples. *The Canadian Journal of Statistics*, 46, 212–232.

Cai, S., Chen, J., & Zidek, J. V. (2017). Hypothesis testing in the presence of multiple samples under density ratio models. *Statistica Sinica*, 27, 761–783.

Chen, J. & Liu, Y. (2013). Quantile and quantile-function estimations under density ratio model. *The Annals of Statistics*, 41, 1669–1692.

Chen, B., Li, P., Qin, J., & Yu, T. (2016). Using a monotonic density ratio model to find the asymptotically optimal combination of multiple diagnostic tests. *Journal of the American Statistical Association*, 111, 861–874.

Fluss, R., Faraggi, D., & Reiser, B. (2005). Estimation of the Youden index and its associated cutoff point. *Biometrical Journal*, 47, 458–472.
Gulick, R. M., Hu, X. J., Fiscus, S. A., Fletcher, C. V., Haubrich, R., Cheng, H., Edward, A., Lagakos, S. W., Swanstrom, R., Freimuth, W., Snyder, S., Mills, C., Fischl, M., Pettinelli, C., & Katzenstein, D. (2000). Randomized study of saquinavir with ritonavir or nelfinavir together with delavirdine, adeovir or both in human immunodeficiency virus-infected adults with virologic failure on indinavir: AIDS Clinical Trials Group Study 359. *The Journal of Infectious Diseases*, 182, 1375–1384.

Hsieh, F. & Turnbull, B. W. (1996). Nonparametric methods for evaluating diagnostic tests. *Statistica Sinica*, 6, 47–62.

Jiang, S. & Tu, D. (2012). Inference on the probability $P(T_1 < T_2)$ as a measurement of treatment effect under a density ratio model and random censoring. *Computational Statistics & Data Analysis*, 56, 1069–1078.

Krzanowski, W. J. & Hand, D. J. (2009). *ROC Curves for Continuous Data*. Chapman & Hall/CRC, London.

Owen, A. B. (2001). *Empirical Likelihood*. Chapman & Hall/CRC, Boca Raton.

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

Pepe, M. S. (2003). *The Statistical Evaluation of Medical Tests for Classification and Prediction*. Oxford University Press, Oxford.

Percy, M. E., Andrews, D. F., & Thompson, M. W. (1982). Duchenne muscular dystrophy carrier detection using logistic discrimination: Serum creatine kinase, hemopexin, pyruvate kinase, and lactate dehydrogenase in combination. *American Journal of Medical Genetics*, 13, 27–38.

Qin, J. (2017). *Biased Sampling, Over-identified Parameter Problems and Beyond*. Springer, Singapore.

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

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

Qin, G. & Zhou, X.-H. (2006). Empirical likelihood inference for the area under the ROC curve. *Biometrics*, 62, 613–622.

Ruopp, M. D., Perkins, N. J., Whitcomb, B. W., & Schisterman, E. F. (2008). Youden index and optimal cut-point estimated from observations affected by a lower limit of detection. *Biometrical Journal*, 50, 419–430.

Schisterman, E. F. & Perkins, N. (2007). Confidence intervals for the Youden index and corresponding optimal cut-point. *Communications in Statistics-Simulation and Computation*, 36, 549–563.

Shan, G. (2015). Improved confidence intervals for the Youden index. *PLOS One*, 10, 73–81.

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

Wan, S. & Zhang, B. (2008). Comparing correlated ROC curves for continuous diagnostic tests under density ratio models. *Computational Statistics & Data Analysis*, 53, 233–245.

Wang, C. (2017). Empirical Likelihood and Bootstrap Inference with Constraints. PhD thesis, UWSpace, http://hdl.handle.net/10012/11204.

Wang, C., Marriott, P., & Li, P. (2017a). Testing homogeneity for multiple nonnegative distributions with excess zero observations. *Computational Statistics & Data Analysis*, 114, 146–157.

Wang, C., Marriott, P., & Li, P. (2018). Semiparametric inference on the means of multiple nonnegative distributions with excess zero observations. *Journal of Multivariate Analysis*, 166, 182–197.

Wang, D., Tian, L., & Zhao, Y. (2017b). Smoothed empirical likelihood for the Youden index. *Computational Statistics & Data Analysis*, 115, 1–10.

Wang, S. & Zhang, B. (2014). Semiparametric empirical likelihood confidence intervals for AUC under a density ratio model. *Computational Statistics & Data Analysis*, 70, 101–115.

Yin, J. & Tian, L. (2014a). Joint inference about sensitivity and specificity at the optimal cut-off point associated with Youden index. *Computational Statistics & Data Analysis*, 77, 1–13.

Yin, J. & Tian, L. (2014b). Optimal linear combinations of multiple diagnostic biomarkers based on Youden index. *Statistics in Medicine*, 33, 1426–1440.

Youden, W. J. (1950). Index for rating diagnostic tests. *Cancer*, 3, 32–35.

Zhang, B. (2006). A semiparametric hypothesis testing procedure for the ROC curve area under a density ratio model. *Computational Statistics & Data Analysis*, 50, 1855–1876.

DOI: 10.1002/cjs.11600 The Canadian Journal of Statistics / La revue canadienne de statistique
Zhang, D. & Zhang, B. (2014). Semiparametric empirical likelihood confidence intervals for the difference of areas under two correlated ROC curves under density ratio model. Biometrical Journal, 56, 678–696.

Zhou, X.-H. & McClish, D. K. (2002). Statistical Methods in Diagnostic Medicine. John Wiley & Sons, New York.

Zhou, H. & Qin, G. (2012). New nonparametric confidence intervals for the Youden index. Journal of Biopharmaceutical Statistics, 22, 1244–1257.

Zhuang, W., Hu, B., & Chen, J. (2019). Semiparametric inference for the dominance index under the density ratio model. Biometrika, 106, 229–241.

Zou, K. H., Liu, A., Bandos, A. I., Ohno-Machado, L., & Rockette, H. E. (2011). Statistical Evaluation of Diagnostic Performance: Topics in ROC Analysis. CRC Press, Boca Raton.

Received 8 May 2020
Accepted 24 September 2020