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GENERALIZED CONFIDENCE INTERVALS FOR PARTIAL YOUDEN INDEX AND ITS CORRESPONDING OPTIMAL CUT-OFF POINT

by

CHENXUE LI

Under the Direction of Gengsheng Qin

ABSTRACT

In the field of diagnostic test studies, the accuracy of a diagnostic test is essential in evaluating the performance of the test. The receiver operating characteristic (ROC) curve and the area under the curve (AUC) are widely used in such evaluation procedures. Meanwhile, the Youden index is also introduced into practice to measure the accuracy of the diagnostic test from another aspect. The Youden index maximizes the sum of sensitivity and specificity, assuring decent true positive and negative rates. It draws one's attention due to its merit of finding the optimal cut-off points of biomarkers. Similar to Partial ROC, a new index, called "Partial Youden index" can be defined as an extension of Youden's Index. It is more meaningful than regular Youden index since the regular one is just a special case of the Partial Youden Index. In this thesis, we focus on construction of generalized confidence intervals for the Partial Youden Index and its corresponding optimal cut-off points. Extensive simulation studies are conducted to evaluate the finite sample performances of the new intervals.

INDEX WORDS: Diagnostic test, Sensitivity, Specificity, Partial-ROC, Youden Index, Partial Youden index, Optimal cut-off point, Generalized Pivotal Quantities, Generalized confidence interval

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by

CHENXUE LI

A Thesis Submitted in Partial Fulfillment of the Requirements for the Degree of

Master of Sciences

in the College of Arts and Sciences

Georgia State University

2013

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2013

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December 2013

DEDICATION

This dissertation is dedicated to my parents, my advisor and my aunt and uncle.

ACKNOWLEDGEMENTS

This dissertation work would not have been possible without the support of many people. I want to express my gratitude to my advisor Professor Qin, my friends Yanan Yin, Jun Xia, Michael Boring and Bing Liu, who give me so many supports and help.

TABLE OF CONTENTS

ACKNOWLEDGEMENTS . . . . . **v**

LIST OF TABLES . . . . . **viii**

LIST OF FIGURES . . . . . **x**

LIST OF ABBREVIATIONS . . . . . **xi**

PART 1 INTRODUCTION **1**

1.1 Diagnostic tests 1

1.2 Youden Index and Partial Youden Index 3

1.3 Existing estimations for Youden Index 6

1.4 Purpose of this thesis 7

PART 2 METHODOLOGY **8**

2.1 Preliminaries 8

2.1.1 Some useful Generalized Pivotal Quantities 9

2.2 GPQ method for Partial YI and its optimal cut-off point 11

2.2.1 Diagnostic curve 11

2.2.2 GPQ method for Partial Youden's Index 11

PART 3 SIMULATION STUDY **14**

PART 4 A REAL EXAMPLE **16**

4.1 Inferences for biomarkers "CA-125" and "CA-19-9" 16

PART 5 SUMMARY AND DISCUSSION **18**

REFERENCES **20**

APPENDICES **23**

Appendix A SIMULATION RESULTS TABLES **23**

LIST OF TABLES

Table A.1 The coverage probabilities and mean lengths of the 90% confidence interval for the Partial Youden's index J_{p_1,p_2}. 23

Table A.2 The coverage probabilities and mean lengths of the 90% confidence interval for the Partial Youden's index J_{p_1,p_2}.(continued) 24

Table A.3 The coverage probabilities and mean lengths of the 90% confidence interval for the Partial Youden's index J_{p_1,p_2}.(continued) 25

Table A.4 The coverage probabilities and mean lengths of the 90% confidence interval for the Partial Youden's index J_{p_1,p_2}.(continued) 26

Table A.5 The coverage probabilities and mean lengths of the 90% confidence interval for the optimal cut-off points c_{po}. 27

Table A.6 The coverage probabilities and mean lengths of the 90% confidence interval for the optimal cut-off points c_{po}.(continued) 28

Table A.7 The coverage probabilities and mean lengths of the 90% confidence interval for the optimal cut-off points c_{po}.(continued) 29

Table A.8 The coverage probabilities and mean lengths of the 90% confidence interval for the optimal cut-off points c_{po}.(continued) 30

Table A.9 The coverage probabilities and mean lengths of the 95% confidence interval for the Partial Youden's index J_{p_1,p_2}. 31

Table A.10 The coverage probabilities and mean lengths of the 95% confidence interval for the Partial Youden's index J_{p_1,p_2}.(continued) 32

Table A.11 The coverage probabilities and mean lengths of the 95% confidence interval for the Partial Youden's index J_{p_1,p_2}.(continued) 33

Table A.12 The coverage probabilities and mean lengths of the 95% confidence interval for the Partial Youden's index J_{p_1,p_2}.(continued) 34

Table A.13 The coverage probabilities and mean lengths of the 95% confidence interval for the optimal cut-off points c_{po}. 35

Table A.14 The coverage probabilities and mean lengths of the 95% confidence interval for the optimal cut-off points c_{po}.(continued) 36

Table A.15 The coverage probabilities and mean lengths of the 95% confidence interval for the optimal cut-off points c_{po}.(continued) 37

Table A.16 The coverage probabilities and mean lengths of the 95% confidence interval for the optimal cut-off points c_{po}.(continued) 38

LIST OF FIGURES

Figure 2.1 Example of Diagnostic Curves (1) 12

Figure 2.2 Example of Diagnostic Curves (2) 12

LIST OF ABBREVIATIONS

- ROC - Receiver Operating Characteristic
- AUC - Area Under The Curve
- GPQ - Generalized Pivotal Quantities
- FN - False Negative
- FP - False Positive
- YI - Youden Index
- True Positive Rate - TPR
- False Negative Rate - FNR
- True Negative Rate - TNR
- False Positive Rate - FPR
- Partial ROC - PROC
- Partial AUC - PAUC
- Diagnostic Curve - DC

PART 1

INTRODUCTION

1.1 Diagnostic tests

Diagnosis is one of the most essential procedures in medical services. When physicians assign proper treatments or write prescriptions to patients, they rely on the diagnostic test results.

Accordingly, the accuracy of the diagnosis of diseases is important. Undoubtedly, biopsy is one of the most reliable diagnostic methods, and therefore is known as a "gold standar". However the costs are significant, for instance, extreme pain, tissue removal, neuro damage, operational costs and so on. As a result, physicians or biological scientists often use biomarkers or body symptoms as the indicators of a person's health status. For diagnostic tests with binary outcomes, the person will be classified into either a healthy group or diseased group based on a screening test method. Screening test methods are widely used to discriminate diseased people from non-diseased people. Only when a diagnostic process can truly distinguish between the diseased and the healthy individuals, can it be viewed as perfectly accurate.

As we all know, the "perfection" is hard to achieve given that the "gold standard" cost too much. A compromise is to make diagnosis according to biomarkers or body symptoms. Since diagnostic error is unavoidable, it is statisticians' role to evaluate the accuracy of diagnostic tests. False negative (FN) errors and false positive (FP) errors are the two types of errors derived from diagnostic test with binary outcomes. An false negative error refers to classifying a diseased individual as non-diseased; a false positive error refers to classifying a non-diseased individual as diseased.

In this thesis, we will consider the circumstances where diagnostic test results are binary and the biomarker test results are continuous, which is the majority in reality.

So far, some well-known measurements of diagnostic accuracy include sensitivity, specificity [1], the Receiver Operating Characteristic (ROC) curve, the area under the ROC curve (AUC) and Youden Index (YI). Without loss of generality, we assume that higher test values indicate higher probability of the disease. Otherwise, we take the opposite of the results. Usually, there is a given criterion value "c" (we also call it threshold or cut-off point), and any individual who has a test result higher than "c" belongs to diseased group. Otherwise, they belong to non-diseased group.

Sensitivity refers to the probability that a truly diseased subject is correctly classified into the diseased group. In other words, the sensitivity is the probability that the diseased subject's test result is larger than c. Hence, we also call it the true positive rate (TPR). The complement of true positive rate error rate is false negative rate (FNR). It is defined as 1-TPR. Similarly, the specificity, refers to the probability that a truly non-diseased subject is correctly grouped into the non-diseased group. In other words, the probability that a truly healthy subject has a test result less than c. We also call it true negative rate (TNR), and the relative error is the false positive rate (FPR), which equals 1-TNR.

It is obvious that sensitivity and specificity can only evaluate the test's accuracy at a certain threshold. They are "local" measurements for biomarker or diagnostic tests.ROC curves are defined as an extension of these measurements.

ROC curves, which are constructed by plotting "1-specificity" against "sensitivity" at all possible cut-off points, have been commonly used for evaluating the performance of diagnostic tests at a "global" scale. A perfect diagnostic test has an ROC curve starting from the origin, going straight to (0, 1), then turning right at ninety degrees and ending at (1, 1). However that is the ideal case. The curve clearly demonstrates the trade-off relationship between TPR and FPR, and it also shows the importance of the choice of cut-off points.

As a summary index of the ROC curve, the area under the ROC curve (AUC) has been widely used. It evaluates the overall discriminating ability of the biomarker as a quantitative measurement ([2], [3], [4]). In the ideal situation, AUC has a value of 1.

Although the ROC curve has many advantages in summarizing the accuracy of a di-

agnostic test, it also has limitations. In some circumstances, ROC curve might be used to represent test performance on a truncated range of clinically relevant values of FPR, or if one wished to exclude those parts of the ROC space where study data are sparse [5]. The ROC curve extends beyond the clinically relevant area of potential clinical interpretation. Hence, the concept of partial AUC ($PAUC$) were proposed. McClish (1989 [6]), Thompson and Zucchini (1989 [7]), and Jiang et al (1996 [8]), focused on partial AUC statistical inferences and gained popularity (Bakera and Pinsky, 2001 [9]). The value of partial AUC analysis has been recognized and several methods have been developed. With proper binormal model checking, McClish ([6], [10]) provided a method for comparing portion of ROC curves. Based on McClish's work, Jiang et al. ([8]) proposed a partial area index for highly sensitive diagnostic tests (Dong D. Zhang et al. [11]). Also, Lori E. Dodd, and Margaret S. Pepe (2003 [12]) interpreted partial AUC from probabilistic perspective in terms of a nonparametric estimator. All these papers show the significance of PAUC, which motivates us to focus on partial case.

However, neither the AUC nor the PAUC can provide any information about the cut-off point with desired sensitivity/specificity, which also should be considered in evaluating the test accuracy.

1.2 Youden Index and Partial Youden Index

A wise choice of the cut-off point is an important implementation for a test. As a result, several methods have been proposed for the statisticians to choose the optimal cut-off points. E.g. "CB" (cost-benefit method); "MinValueSp" (a minimum value set for Specificity); "MinValueSe" (a minimum value set for Sensitivity); "RangeSp" (a range of values set for Specificity); "RangeSe" (a range of values set for Sensitivity) and so on. Details could be found in R program, package 'Optimal Cutpoints' (Miller and Siegmund, 1982 [13], Altman, et al., 1994 [14]).

Here we focus on Youden Index method. The Youden index (J) was first introduced by Youden [15] in 1950. Clearly, since both greater sensitivity and specificity are desired,

Schisterman and Perkins [16] pointed out that the optimal threshold for the positive test result of a disease should be the threshold leading to the maximum of the sum of TPR and TNR. At the same time, this optimal cut-off point also guarantees minimization of the sum of FPR and FNR, and Youden's Index illustrates this simply and clearly. It is defined as follows:

$$J = \max_c \{sensitivity(c) + specificity(c) - 1\} \tag{1.1}$$

$$= sensitivity(c_0) + specificity(c_0) - 1 \tag{1.2}$$

where c_0 is the optimal cut-point of the test results.

J is a biomarker's maximum differentiating ability when equal weight is given to sensitivity and specificity, with J ranging from 0 to 1 where 0 indicates the test has no discriminating ability and 1 indicates the test is perfect (Fluss et al., 2005 [17]). It not only supplies a method to find an optimal cut-off point, but it also provides a numerical summary of the classification likelihood of the test. From a graphical perspective, Youden's Index is the maximum vertical distance between the ROC curve and the diagonal chance line, which is in accord with the differentiating capacity of the diagnosis. This index posses several remarkable features, such as it is independent of the relative/absolute sizes of the diseased and non-diseased groups, and all tests that share the same index make the same total number of misclassifications per hundred patients (Youden 1950 [15]).

As Youden's Index has such good features, we expand it into a more general case in which the partial ROC curve is considered, and we name it "Partial Youden's Index".

As mentioned above, the ROC curve is constructed by plotting "1-specificity" against "sensitivity" at all possible cut-off points. Let X denote the test result from a non-diseased population and X_i $(i = 1, 2, 3, \ldots, n)$ *i.i.d.* where X_i's are observations for X with distribution $F(x)$. Let Y denote the test result from diseased population and Y_j's $(j = 1, 2, 3, \ldots, m)$ are *i.i.d.* observations for Y with distribution $G(y)$. c is the cut-off point, then, according to

the definition,we have

$$sensitivity(c) = P(Y \geq c) = 1 - G(c) \tag{1.3}$$

$$specifity(c) = P(X \leq c) = F(c) \tag{1.4}$$

Since Youden Index is related to sensitivity and specificity (see eq.1.1,1.2),so it also can be written as follows:

$$J = \max_c \{1 - G(c) + F(c) - 1\} \tag{1.5}$$

$$= \max_c \{F(c) - G(c)\} \tag{1.6}$$

$$= F(c_0) - G(c_0) \tag{1.7}$$

where c_0 is the optimal cut-point of the test results. We find this optimal c_0 on a scale of all possible cut-off points,i.e. the full ROC curve is considered in this case.

Here in the PROC case, high specificity or high sensitivity are desired. Dating back to 2003, Partial Area under the ROC curve was first proposed by Lori E. Dodd et. al(2003). He pointed out that the partial AUC was an alternative measure to the full AUC. When using the partial AUC, one considers only those regions of the ROC space where data have been observed, or which correspond to clinically relevant values of test sensitivity or specificity [12].

Similarly, our motivation is to consider the Youden Index under the case when a minimum FPR(1-specificity) is guaranteed by given $FPR \geq p_1$, while a high TPR (sensitivity) is wanted by given $FPR \leq p_2$.

The limitation is given by $1 - p_2 \leq specificity(c) \leq 1 - p_1$ (where $p_1 \leq p_2$ are FPRs). Since $specificity(c)$ is actually a cumulative distribution function $(c.d.f)$ $F(c)$, so we can

use inverse function to find the limitation for cut-off points,

$$c_1 = F^{-1}(1 - p_1) \tag{1.8}$$

$$c_2 = F^{-1}(1 - p_2) \tag{1.9}$$

$$c_2 \leq c \leq c_1 \tag{1.10}$$

Now, the definition of partial Youden Index can be given by

$$J_{p_1,p_2} = \max_{c_2 \leq c \leq c_1} \{sensitivity(c) + specificity(c) - 1\} \tag{1.11}$$

$$= sensitivity(c_{po}) + specificity(c_{po}) - 1 \tag{1.12}$$

$$= F(c_{po}) - G(c_{po}) \tag{1.13}$$

where c_{po} is the optimal cut-off point for partial Youden Index. When $p_1 = 0, p_2 = 1$, then $c_1 = \infty, c_2 = 0$.

1.3 Existing estimations for Youden Index

We can easily tell from the expressions above, both Youden Index and Partial Youden Index are functions of sensitivity and specificity depending on the underlying distribution of diseased and non-diseased populations $F(x)$ and $G(y)$. Myriad methods have been applied to Youden Index estimation, including parametric and non-parametric techiques. Most of them have an assumption about their underlying distributions, such as binormal distributions. Fluss et al. [17] proposed a parametric point estimate for Youden's index. Schisterman and Perkins [16] provided parametric confidence interval estimates for the index based on the Delta method (Shao [18]) for the index and offered nonparametric approaches.

Hsieh and Turnbull [19] studied the nonparametric point estimates for the index based on the empirical and kernel estimates for the underlying distributions without parametric assumptions for the underlying distributions. They provided asymptotic properties of the two estimates; however, the asymptotic variances for the empirical estimate of Youden's

index is still unclear, thus confidence intervals for the Youden index cannot be constructed directly. Some studies (e.g., Faraggi [20]) considered constructing non-parametric confidence intervals for the Youden's index and the corresponding cutoff points. Zhou and Qin [21] focused on construction of non-parametric confidence intervals for the Youden index and provided two new non-parametric intervals for the index based on Agresti and Coull's [22] adjusted estimate (AC adjustment) for a binomial proportion.

1.4 Purpose of this thesis

In this thesis, we focus on construction of generalized confidence intervals for the Partial Youden Index and its corresponding cut-off points. First of all, we will introduce some basic knowledge about diagnostic tests, Youden Index and Partial Youden Index. In the second section, we construct the exact confidence interval (ECI) for Partial Youden's index and correspongding cut-off pionts based on normal assumptions for test result with Generalized Pivotal Quantitives (GPQs, see Weerahandi [23]). The third section will show extensive simulation studies results to evaluate the finite sample performances of the new intervals. At last, our proposed method will be applied on a real example.

PART 2

METHODOLOGY

2.1 Preliminaries

In the following, we will briefly review the basic concept of the generalized confidence interval proposed by Weerahandi (1993 [23]).

Suppose that Y is a random variable whose distribution depends on (θ, δ), where θ is a parameter of interest and δ is a nuisance parameter. Let y be the observed value of Y. A generalized pivotal quantity $R(Y; y, \theta, \delta)$, a function of Y, y, θ, and δ, for interval estimation, defined in Weerahandi (1993), satisfies the following two conditions:

(1) $R(Y; y, \theta, \delta)$ has a distribution free of all unknown parameters.

(2) The value of $R(Y; y, \theta, \delta)$ at $Y = y$ is θ, the parameter of interest

Generalized Pivotal Quantities method is based on normal assumptions, which means we assume the underlying distributions of non-diseased and diseased populations $F(x)$ and $G(y)$ are $N(\mu_x, \sigma_x^2), N(\mu_y, \sigma_y^2)$, respectively. X and Y are independent.

Without loss of generality, we assume that $\mu_x < \mu_y$; otherwise take the negative of the biomarker value. First of all, point estimates for the cut-off point and Youden's Index are given in Schisterman and Perkins (2007) [16] paper, the optimal cut-off point maximizes the expression

$$h(c) = F(c) - G(c)$$

Then we make

$$h'(c) = f(c) - g(c) = 0$$

and solve for the optimal cut-off point, where $f(c)$ and $g(c)$ are density functions of normal

distributions $N(\mu_x, \sigma_x^2), N(\mu_y, \sigma_y^2)$.

$$c_0 = \frac{\mu_x(b^2-1) - a + b\sqrt{a^2 + (b^2-1)\sigma_x^2 \ln b^2}}{b^2-1} \tag{2.1}$$

and

$$J = \Phi\left(\frac{\mu_y - c_0}{\sigma_y}\right) + \Phi\left(\frac{c_0 - \mu_x}{\sigma_x}\right) \tag{2.2}$$

where $a = \mu_y - \mu_x, b = \frac{\sigma_y}{\sigma_x}$, and $\Phi(\cdot)$ denotes the standard normal cumulative distribution function.

When variances are equal, c_0 is undefined and it can be replaced by

$$c_0 = \frac{\mu_x + \mu_y}{2} \tag{2.3}$$

which is the limit of (2.1) as $b \to 1$.

2.1.1 Some useful Generalized Pivotal Quantities

$\bar{X}$, $\bar{Y}$ are the sample means and S_x^2, S_y^2 are sample variances of the non-diseased and diseased populations. Let $\bar{x}$, $\bar{y}$ and s_x^2, s_y^2 be the observed values of $\bar{X}$, $\bar{Y}$ and S_x^2, S_y^2 respectively. The generalized pivotal quantities for estimating μ_x, μ_y are

$$R_{\mu_x} = \bar{x} - \left(\frac{\bar{X} - \mu_x}{\sigma_x/\sqrt{n}}\right)\frac{\sigma_x}{S_x}\frac{s_x}{\sqrt{n}} = \bar{x} - \frac{Z_x}{\sqrt{V_x/(n-1)}}\frac{s_x}{\sqrt{n}} = \bar{x} - t_x\frac{s_x}{\sqrt{n}} \tag{2.4}$$

$$R_{\mu_y} = \bar{y} - \left(\frac{\bar{Y} - \mu_y}{\sigma_y/\sqrt{m}}\right)\frac{\sigma_y}{S_y}\frac{s_y}{\sqrt{m}} = \bar{y} - \frac{Z_y}{\sqrt{V_y/(m-1)}}\frac{s_y}{\sqrt{m}} = \bar{y} - t_y\frac{s_y}{\sqrt{m}} \tag{2.5}$$

where $Z_x = \frac{\sqrt{n}(\bar{X}-\mu_x)}{\sigma_x} \sim N(0,1), Z_y = \frac{\sqrt{m}(\bar{Y}-\mu_y)}{\sigma_y} \sim N(0,1), V_x = \frac{(n-1)S_x^2}{\sigma_x^2} \sim \chi^2_{n-1}, V_y = \frac{(m-1)S_y^2}{\sigma_y^2} \sim \chi^2_{m-1}$ and $t_x = \frac{Z_x}{\sqrt{V_x/(n-1)}}, t_y = \frac{Z_y}{\sqrt{V_y/(m-1)}}$ follow Student's t-distribution with degrees of freedom $n-1, m-1$, respectively.

The generalized pivotal quantities for σ_x^2, σ_y^2 are given by

$$R_{\sigma_x^2} = \frac{\sigma_x^2}{(n-1)S_x^2}(n-1)s_x^2 = \frac{(n-1)s_x^2}{V_x}, \tag{2.6}$$

$$R_{\sigma_y^2} = \frac{\sigma_y^2}{(m-1)S_y^2}(m-1)s_y^2 = \frac{(m-1)s_y^2}{V_y}, \tag{2.7}$$

respectively.

The generalized pivotal quantities for σ_x, σ_y are defined as:$R_{\sigma_x} = \sqrt{R_{\sigma_x^2}}, R_{\sigma_y} = \sqrt{R_{\sigma_y^2}}$.

Let

$$R_a = R_{\mu_y} - R_{\mu_x}, \quad R_b = \frac{R_{\sigma_y}}{R_{\sigma_x}}$$

be the GPQs for a, b.

Then by plugging in $R_a, R_b, R_{\mu_x}, R_{\sigma_x^2}$, we can get R_J, R_{c_0}, which are the GPQs for c_0 and J.

$$R_{c_0} = \frac{R_{\mu_x}(R_b^2 - 1) - R_a + R_b\sqrt{R_a^2 + (R_b^2 - 1)R_{\sigma_x^2}\ln R_b^2}}{R_b^2 - 1}. \tag{2.8}$$

When the variances are equal,

$$R_{c_0} = \frac{R_{\mu_x} + R_{\mu_y}}{2} \tag{2.9}$$

Then, by substitution,

$$R_J = \Phi\left(\frac{R_{\mu_y} - R_{c_0}}{R_{\sigma_y}}\right) + \Phi\left(\frac{R_{c_0} - R_{\mu_x}}{R_{\sigma_x}}\right) - 1. \tag{2.10}$$

(Lai et al. [24]).

2.2 GPQ method for Partial YI and its optimal cut-off point

To start with, "diagnostic curve" will be introduced as a tool to find the optimal cut-off point for partial Youden Index (Zhou, 2011 [21]).

2.2.1 Diagnostic curve

Diagnostic curve (DC) is highly related to Youden's Index. Youden's Index is the maximized value of {*sensitiviy(c)+specificity(c)*-1}, and {*sensitiviy(c)+specificity(c)*-1} itself is defined as the Diagnostic curve (DC). DC measures the diagnostic accuracy of the test at any given cut-off value c. Hence, $h(c)$ is the expression of DC in this thesis.

It is significant for us to find the optimal cut-off point for partial Youden's Index. Once p_1 and p_2 are given, c_1 and c_2 are determined.

Since we usually assume the non-diseased group follows a standard normal distribution, we only consider when $X \sim N(0, 1)$. Let's see some examples of DC when $F(x)$ is standard normal distribution (figure 2.1, 2.2), and $G(y)$ is any other regular normal distribution with stochastic order $F(x) < G(y)$.

Then, we have 3 situations concerned:

1. The regular c_0 is located between the given cut-off point limit $(c_2, c_1), c_{po} = c_0$;
2. The regular c_0 is located to the left side of the given cut-off point limit $(c_2, c_1), c_{po} = c_2$;
3. The regular c_0 is located to the right side of the given cut-off point limit $(c_2, c_1), c_{po} = c_1$;

In conclusion: c_{po}=median(c_0, c_1, c_2).

2.2.2 GPQ method for Partial Youden's Index

Based on the GPQ, DC and generalized confidence interval for YI knowledge, we get the generalized confidence interval for partial Youden's Index.

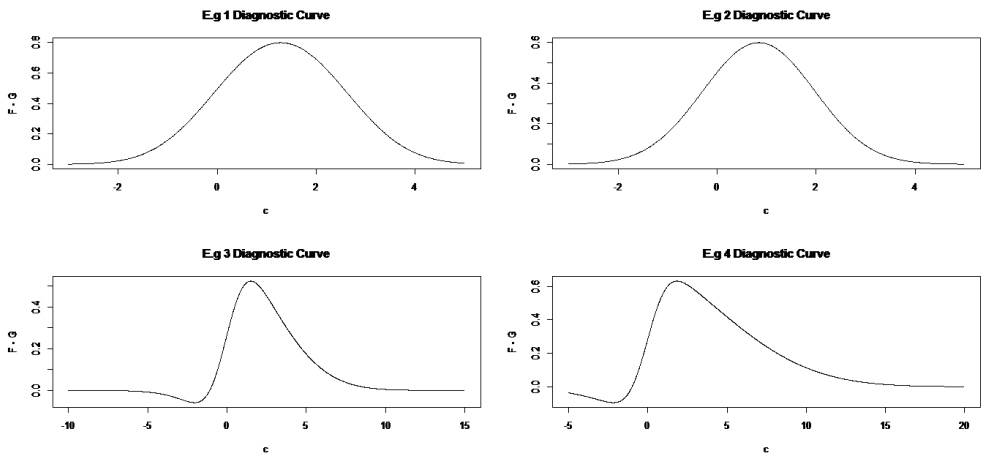

Figure (2.1) Example of Diagnostic Curves (1)

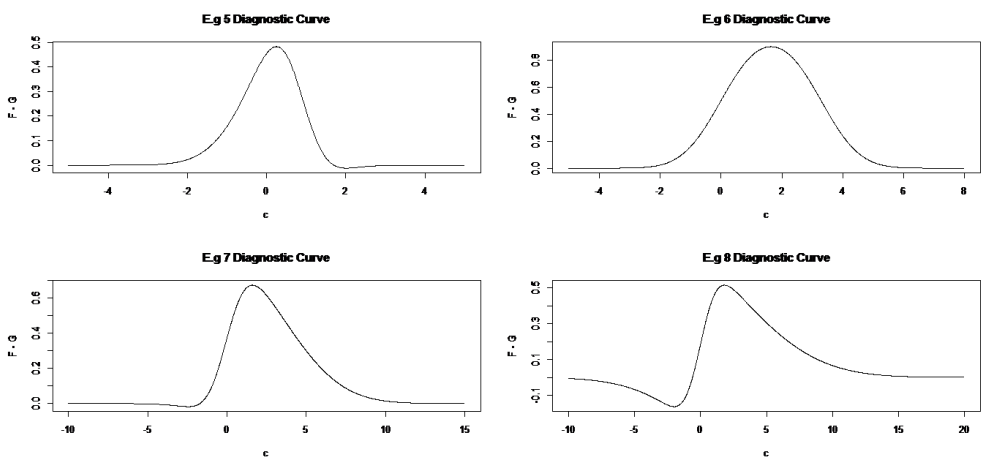

Figure (2.2) Example of Diagnostic Curves (2)

Estimation for c_1 and c_2, since we have the following expressions,

$$c_1 = F^{-1}(1 - p_1), \quad c_2 = F^{-1}(1 - p_2). \tag{2.11}$$

Here, $F(x)$ is $N(\mu_x, \sigma_x^2)$ under normal assumption.

$$c_1 = \sigma_x \Phi^{-1}(1 - p_1) + \mu_x, \quad c_2 = \sigma_x \Phi^{-1}(1 - p_2) + \mu_x. \tag{2.12}$$

Consequently, $R_{c_1} = R_{\sigma_x}\Phi^{-1}(1-p_1) + R_{\mu_x}, \quad R_{c_2} = R_{\sigma_x}\Phi^{-1}(1-p_2) + R_{\mu_x}$.

Algorithm:

For a given data set including $x_1, \ldots, x_n$, and $y_1, \ldots, y_m$, the generalized confidence intervals for partial Youden's Index and its corresponding cut off points are based on the following algorithm:

1. Compute the sample mean $\bar{x}, \bar{y}$ and sample variance s_x^2, s_y^2.

2. For $k = 1, \ldots, K$

   - Generate t_{n-1} and t_{m-1};
   - Generate V_x, V_y from $\chi^2_{n-1}, \chi^2_{m-1}$;
   - Compute $R_{\mu_x}, R_{\mu_y}, R_{\sigma_x}$, and R_{σ_y} according to equation (2.4-2.7);
   - Compute $R_{c_0}, R_{c_1}, and R_{c_2}$, assign $R_{c_{po}} = median(R_{c_0}, R_{c_1}, R_{c_2})$, according to equation (2.8-2.10);
   - Compute $R_{J_{p_1,p_2}}$ via plugging in the $R_{c_{po}}$.
     (end k loop)

3. Compute the $100\alpha/2$th percentile $R_{J_{p_1,p_2},\alpha/2}$ and the $100(1-\alpha/2)$th percentile $R_{J_{p_1,p_2},(1-\alpha)/2}$ of $R_{J_{p_1,p_2},1}, R_{J_{p_1,p_2},2}, R_{J_{p_1,p_2},3}, \ldots, R_{J_{p_1,p_2},K}$.Then,$\left(R_{J_{p_1,p_2},\alpha/2}, R_{J_{p_1,p_2},(1-\alpha)/2}\right)$ is a $100(1-\alpha)\%$confidence interval of J_{p_1,p_2}.

4. Compute the $100\alpha/2$th percentile $R_{c_{po},\alpha/2}$ and the $100(1-\alpha/2)$th percentile $R_{c_{po},(1-\alpha)/2}$ of $R_{c_{po},1}, R_{c_{po},2}, R_{c_{po},3}, \ldots, R_{c_{po},K}$. Then, $\left(R_{c_{po},\alpha/2}, R_{c_{po},(1-\alpha)/2}\right)$ is a $100(1-\alpha)\%$ confidence interval of c_{po}.

PART 3

SIMULATION STUDY

To evaluate the performance of our method, extensive simulation studies are conducted. Coverage probability and average length of the confidence intervals will be presented as references.

We are interested in small to moderate sample sizes. By setting several scenarios, we can determine how well the method works. Under the normality assumption, control groups were normally distributed with mean $\mu_x = 0$ and variance $\sigma_x^2 = 1$ and the case groups with mean μ_y and variances $\sigma_y^2 = 0.5$. The values for μ_y were chosen to correspond to the true Youden's Index $J = 0.4, 0.6, 0.8, 0.9$. The R program was used to generate 2500 iterations (K=2500) to form the distribution of partial Youden's Index $R_{J_{p_1,p_2}}$ and its corresponding cut off points $R_{c_{po}}$. Choose $p_1 = (0, 0.01, 0.05, 0.1), p_2 = (0.1, 0.2, 0.3)$, and each possible combination of (p_1, p_2) was considered, except for $p_1 = 0.1, p_2 = 0.1$. 1000 iterations were made to compute the coverage probability and average length of the 90% ,95% confidence intervals. We generated samples of sizes $(n, m) = (15, 15), (30, 30), (30, 15), (50, 50)$ with normal distributional assumptions. (30, 15) is set up to detect the unbalanced case.

The simulation results are shown in the Appendix A.

From the results, we can tell the generalized confidence interval for partial Youden's index method works excellent. With the increasing sample sizes, the average lengths of the confidence interval are smaller, but the coverage probability are still excellent around 0.9, and 0.95. As the true Youden index increases, no big difference among each scenarios of the coverage probability and average length when other parameters remain the same. For partial Youden Index J_{p_1,p_2}, the results are stable even when p_1 and p_2 are close. The generalized pivotal quantity method works great on Partial Youden's Index, the coverage probability appears to be good no matter what are the means for the diseased group. However, the

method seems to be over-covered for the corresponding cut-off values, especially when the true Youden's Index is 0.8, and 0.9.

Generally speaking, the generalized confidence interval methods perform well both on J_{p_1,p_2} and c_{po}. The generalized confidence intervals for J_{p_1,p_2} and c_{po} is an available method. Since there is no other relative work have been done on J_{p_1,p_2} and c_{po} before, our method is an initiative and is top choice so far. More inferential methods are ready to be proposed.

PART 4

A REAL EXAMPLE

4.1 Inferences for biomarkers "CA-125" and "CA-19-9"

Now, we apply our method on a real example. The pancreatic cancer data were discussed by Wieand et al 1989 [25]. The data sets are the outcomes of two biomarkers "CA-125" and "CA-19-9", which include tests results from 51 "control" patients and 90 "case" patients.

Wieand et al. (1989) plotted the ROC curves of "CA-125" and "CA-19-9", and demonstrated that there were some differences between the two curves when the specificity falls in (0.8, 1) [26]. This motivates us to focus on this interval to detect the diagnostic ability of partial Youden Index.

Specificity falls in (0.8, 1) corresponds to $p_1 = 0, p_2 = 0.2$. Since the original data are not normally distributed, so we use Box-Cox transformation with the power parameter $\phi = -0.425$ to the "CA-125" test results, and $\phi = -0.015$ to the "CA-19-9" tests results. Then the transformed data would follow normal distribution.

We use the same iteration settings for the real example, and get the $90\%, 95\%$ generalized confidence interval for partial Youden Index $J_{0,0.2}$ and its corresponding cut-off values. Based on this results, we will recommend a better biomarker for diagnosing pancreatic cancer in terms of partial Youden Index. Then we compare our conclusions with those previous results.

Our results show that: $90\%, 95\%$ confidence intervals of "CA-125" biomarker are $(0.13166, 0.38364)_{90\%}$, $(0.10971, 0.40081)_{95\%}$ for J_{p_1,p_2} respectively, and $(19.2118, 30.7676)_{90\%}$, $(18.4289, 32.5049)_{95\%}$ for c_{po} respectively. The results of "CA-19-9" are much better than "CA-125" which are $(0.60737, 0.75765)_{90\%}$, $(0.58750, 0.76938)_{95\%}$ for J_{p_1,p_2} and $(31.7701, 67.2277)_{90\%}$, $(30.1831, 74.0393)_{95\%}$ for c_{po}.

Apparently, the J_{p_1,p_2} of "CA-19-9" shows "CA-19-9" has higher diagnostic accuracy to test pancreatic cancer than biomarker "CA-125". Therefore, we recommend "CA-19-9",

which coincide with the results in Huang et al's paper[26]. Also, based on our proposed method, we can get the confidence intervals for the optimal cut off points, and this "information" can not be obtained by ROC methods.

PART 5

SUMMARY AND DISCUSSION

In this thesis, we propose a new concept "Partial Youden's Index" and provide the procedure to find a generalized confidence interval for PYI and its corresponding cut-off point. Our estimation method is derived from GPQ method. PYI maintains merits of YI, which can be a useful tool for finding an optimal cut-off point. In addition, PYI can assure a lower FPR and FNR by adjusting the values of the limits p_1 and p_2. It performs excellent behaviours when the physicians are dealing with the test having requirements on minimum sensitivity or specificity. Extensive simulation studies which concentrated on small to moderate sample sizes show the efficiency of the method.

From the results, we can tell the generalized confidence interval for partial Youden's index method works excellent. With the increasing sample sizes, the average lengths of the confidence interval are smaller, but the coverage probability are still excellent around 0.9 and 0.95 at level 90% and 95% confidence levels. As the true Youden index increases, no big difference among each scenarios of the coverage probability and average length when other parameters remain the same. For partial Youden Index J_{p_1,p_2}, the results are stable even when p_1 and p_2 are close.

Generally speaking, the generalized confidence interval methods perform well both on J_{p_1,p_2} and c_{po}. The generalized confidence interval for J_{p_1,p_2} and c_{po} is an available and reliable method. Since there is no other relative work have been done before on J_{p_1,p_2} and c_{po}, our method is an initiative and is top choice so far. More inferential methods are ready to be proposed.

Actually, more inferential methods could be applied to the new concept "PYI". We only define the generalized confidence interval estimation, which is a parametric method under normal assumption. More work can be done in future. Delta method is also an alternative

parametric method for us. Non-parametric methods for "PYI" can be proposed for future study, borrowing the methods in Zhou & Qin's paper [21]. Mixed models can be generated to see the robustness of the method. Also, so far we have only considered the case that the test outcome is binary; 3-ordinal cases can also be researched.

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Appendix A

SIMULATION RESULTS TABLE

Table (A.1) The coverage probabilities and mean lengths of the 90% confidence interval for the Partial Youden's index J_{p_1,p_2}.

σ	J	p_1	p_2	n	m	cp	al	n	m	cp	al
0.5	0.4	0	0.1	15	15	0.910	0.5263	30	15	0.910	0.4911
			0.2			0.908	0.5722			0.899	0.5445
			0.3			0.919	0.5366			0.914	0.4991
		0.01	0.1			0.910	0.5315			0.927	0.5077
			0.2			0.916	0.5763			0.927	0.5412
			0.3			0.918	0.5415			0.927	0.5001
		0.05	0.1			0.919	0.5212			0.902	0.4935
			0.2			0.901	0.5735			0.920	0.5401
			0.3			0.925	0.5435			0.903	0.4991
		0.1	0.2			0.923	0.5734			0.901	0.5423
			0.3			0.922	0.5400			0.918	0.5002
		0	0.1	30	30	0.904	0.3985	50	50	0.913	0.3210
			0.2			0.925	0.4349			0.918	0.3468
			0.3			0.900	0.3911			0.905	0.3047
		0.01	0.1			0.921	0.3954			0.904	0.3205
			0.2			0.890	0.4312			0.910	0.3462
			0.3			0.904	0.3890			0.898	0.3018
		0.05	0.1			0.918	0.3998			0.911	0.3211
			0.2			0.924	0.4366			0.918	0.3470
			0.3			0.896	0.3903			0.900	0.3032
		0.1	0.2			0.913	0.4353			0.898	0.3444
			0.3			0.917	0.3867			0.890	0.3045

Table (A.2) The coverage probabilities and mean lengths of the 90% confidence interval for the Partial Youden's index J_{p_1,p_2}.(continued)

σ	J	p_1	p_2	n	m	cp	al	n	m	cp	al
0.5	0.6	0	0.1	15	15	0.920	0.6156	30	15	0.910	0.5946
			0.2			0.935	0.5165			0.917	0.4867
			0.3			0.904	0.4429			0.922	0.4086
		0.01	0.1			0.905	0.6141			0.914	0.5971
			0.2			0.926	0.5174			0.917	0.4838
			0.3			0.912	0.4478			0.925	0.3991
		0.05	0.1			0.920	0.6217			0.890	0.5871
			0.2			0.911	0.5212			0.918	0.4872
			0.3			0.907	0.4457			0.914	0.4032
		0.1	0.2			0.904	0.5107			0.911	0.4857
			0.3			0.912	0.4401			0.921	0.4001
		0	0.1	30	30	0.885	0.4706	50	50	0.901	0.3780
			0.2			0.922	0.3602			0.902	0.2764
			0.3			0.896	0.2994			0.917	0.2218
		0.01	0.1			0.907	0.4716			0.894	0.3761
			0.2			0.904	0.3601			0.904	0.2759
			0.3			0.904	0.2963			0.890	0.2202
		0.05	0.1			0.916	0.4751			0.911	0.3803
			0.2			0.903	0.3569			0.915	0.2751
			0.3			0.925	0.2953			0.887	0.2213
		0.1	0.2			0.907	0.3630			0.906	0.2778
			0.3			0.900	0.2932			0.896	0.2205

Table (A.3) The coverage probabilities and mean lengths of the 90% confidence interval for the Partial Youden's index J_{p_1,p_2}.(continued)

σ	J	p_1	p_2	n	m	cp	al	n	m	cp	al
0.5	0.8	0	0.1	15	15	0.918	0.4684	30	15	0.916	0.4334
			0.2			0.914	0.3341			0.917	0.2987
			0.3			0.915	0.2998			0.914	0.2661
		0.01	0.1			0.915	0.4540			0.924	0.4339
			0.2			0.922	0.3312			0.917	0.3001
			0.3			0.935	0.3002			0.917	0.2648
		0.05	0.1			0.924	0.4629			0.917	0.4317
			0.2			0.921	0.3240			0.916	0.2900
			0.3			0.913	0.2930			0.900	0.2622
		0.1	0.2			0.903	0.3026			0.909	0.2663
			0.3			0.922	0.2765			0.911	0.2387
		0	0.1	30	30	0.899	0.3025	50	50	0.910	0.2199
			0.2			0.904	0.2144			0.904	0.1572
			0.3			0.909	0.2057			0.906	0.1564
		0.01	0.1			0.953	0.4716			0.903	0.2176
			0.2			0.902	0.2110			0.897	0.1593
			0.3			0.898	0.2045			0.897	0.1567
		0.05	0.1			0.911	0.3021			0.904	0.2214
			0.2			0.904	0.2102			0.893	0.1584
			0.3			0.920	0.2031			0.880	0.1559
		0.1	0.2			0.899	0.1963			0.919	0.1497
			0.3			0.892	0.1879			0.907	0.1474

Table (A.4) The coverage probabilities and mean lengths of the 90% confidence interval for the Partial Youden's index J_{p_1,p_2}.(continued)

σ	J	p_1	p_2	n	m	cp	al	n	m	cp	al
0.5	0.9	0	0.1	15	15	0.896	0.2767	30	15	0.910	0.2314
			0.2			0.926	0.2187			0.915	0.1910
			0.3			0.914	0.2097			0.913	0.1871
		0.01	0.1			0.904	0.2703			0.895	0.1619
			0.2			0.904	0.2139			0.913	0.1932
			0.3			0.935	0.2081			0.904	0.1866
		0.05	0.1			0.905	0.2535			0.891	0.2349
			0.2			0.925	0.1954			0.916	0.1728
			0.3			0.912	0.1896			0.911	0.1665
		0.1	0.2			0.912	0.1485			0.916	0.1264
			0.3			0.917	0.1507			0.920	0.1251
		0	0.1	30	30	0.919	0.1599	50	50	0.900	0.1127
			0.2			0.907	0.1411			0.905	0.1071
			0.3			0.912	0.1423			0.909	0.1070
		0.01	0.1			0.908	0.1318			0.895	0.1127
			0.2			0.886	0.1387			0.888	0.1074
			0.3			0.899	0.1425			0.897	0.1065
		0.05	0.1			0.897	0.1457			0.895	0.1026
			0.2			0.909	0.1307			0.899	0.0989
			0.3			0.906	0.1278			0.889	0.0993
		0.1	0.2			0.911	0.0895			0.896	0.0643
			0.3			0.901	0.0920			0.900	0.0637

Table (A.5) The coverage probabilities and mean lengths of the 90% confidence interval for the optimal cut-off points c_{po}.

σ	J	p_1	p_2	n	m	cp	al	n	m	cp	al
0.5	0.4	0	0.1	15	15	0.908	1.2799	30	15	0.908	1.2489
			0.2			0.910	1.0785			0.911	1.0689
			0.3			0.911	0.9346			0.919	0.8819
		0.01	0.1			0.914	1.2708			0.926	1.2593
			0.2			0.921	1.1499			0.941	1.0471
			0.3			0.909	0.8901			0.914	0.8645
		0.05	0.1			0.906	1.2509			0.905	1.2365
			0.2			0.905	1.0445			0.922	1.0503
			0.3			0.914	0.8987			0.911	0.8708
		0.1	0.2			0.914	1.0393			0.910	1.0505
			0.3			0.911	0.8791			0.905	0.8639
		0	0.1	30	30	0.911	0.8510	50	50	0.918	0.6448
			0.2			0.906	0.7260			0.896	0.5530
			0.3			0.904	0.6216			0.904	0.4790
		0.01	0.1			0.920	0.8480			0.889	0.6436
			0.2			0.907	0.7167			0.900	0.5555
			0.3			0.894	0.6120			0.890	0.4733
		0.05	0.1			0.902	0.8408			0.895	0.6447
			0.2			0.926	0.7277			0.914	0.5531
			0.3			0.891	0.6089			0.898	0.4774
		0.1	0.2			0.914	0.7220			0.897	0.5513
			0.3			0.916	0.6092			0.886	0.4780

Table (A.6) The coverage probabilities and mean lengths of the 90% confidence interval for the optimal cut-off points c_{po}.(continued)

σ	J	p_1	p_2	n	m	cp	al	n	m	cp	al
0.5	0.6	0	0.1	15	15	0.910	1.2153	30	15	0.914	1.2397
			0.2			0.930	0.9383			0.934	0.9267
			0.3			0.882	0.7428			0.873	0.6931
		0.01	0.1			0.915	1.2144			0.906	1.2499
			0.2			0.930	0.9352			0.922	0.9199
			0.3			0.876	0.7442			0.883	0.6721
		0.05	0.1			0.924	0.1240			0.903	1.2280
			0.2			0.909	0.9400			0.933	0.9256
			0.3			0.890	0.7440			0.899	0.6731
		0.1	0.2			0.918	0.9463			0.909	0.9491
			0.3			0.898	0.7516			0.891	0.6898
		0	0.1	30	30	0.890	0.8426	50	50	0.898	0.6449
			0.2			0.933	0.6412			0.900	0.5038
			0.3			0.876	0.4804			0.904	0.3478
		0.01	0.1			0.913	0.8387			0.887	0.6389
			0.2			0.924	0.6455			0.929	0.5049
			0.3			0.888	0.4731			0.896	0.3470
		0.05	0.1			0.907	0.8437			0.908	0.6462
			0.2			0.908	0.6368			0.907	0.5009
			0.3			0.869	0.4720			0.898	0.3476
		0.1	0.2			0.917	0.6513			0.916	0.5036
			0.3			0.874	0.4730			0.906	0.3458

Table (A.7) The coverage probabilities and mean lengths of the 90% confidence interval for the optimal cut-off points c_{po}.(continued)

σ	J	p_1	p_2	n	m	cp	al	n	m	cp	al
0.5	0.8	0	0.1	15	15	0.928	1.0933	30	15	0.932	1.1181
			0.2			0.921	0.7815			0.948	0.6942
			0.3			0.936	0.7052			0.932	0.5664
		0.01	0.1			0.919	1.0978			0.942	1.0670
			0.2			0.941	0.7884			0.949	0.6979
			0.3			0.927	0.6980			0.928	0.5665
		0.05	0.1			0.922	1.1342			0.931	1.1179
			0.2			0.927	0.8127			0.941	0.7340
			0.3			0.936	0.7316			0.930	0.6162
		0.1	0.2			0.929	0.9054			0.921	0.8500
			0.3			0.928	0.8052			0.912	0.7275
		0	0.1	30	30	0.918	0.7385	50	50	0.922	0.5635
			0.2			0.931	0.4929			0.925	0.3599
			0.3			0.924	0.4592			0.920	0.3487
		0.01	0.1			0.953	0.8418			0.915	0.5585
			0.2			0.934	0.4890			0.928	0.3613
			0.3			0.929	0.2963			0.909	0.3490
		0.05	0.1			0.918	0.7525			0.919	0.5673
			0.2			0.940	0.5006			0.932	0.3642
			0.3			0.932	0.4676			0.933	0.3517
		0.1	0.2			0.925	0.5725			0.936	0.4138
			0.3			0.923	0.5327			0.941	0.4003

Table (A.8) The coverage probabilities and mean lengths of the 90% confidence interval for the optimal cut-off points c_{po}.(continued)

σ	J	p_1	p_2	n	m	cp	al	n	m	cp	al
0.5	0.9	0	0.1	15	15	0.910	0.9572	30	15	0.917	0.8524
			0.2			0.926	0.7945			0.936	0.6535
			0.3			0.933	0.7698			0.934	0.6307
		0.01	0.1			0.926	0.9715			0.931	0.6052
			0.2			0.905	0.8059			0.934	0.6712
			0.3			0.912	0.7869			0.941	0.6484
		0.05	0.1			0.927	1.1606			0.920	1.0663
			0.2			0.920	0.9225			0.936	0.8460
			0.3			0.917	0.9020			0.931	0.8236
		0.1	0.2			0.921	1.0322			0.908	1.0188
			0.3			0.928	1.0088			0.913	0.9906
		0	0.1	30	30	0.930	0.5998	50	50	0.933	0.4328
			0.2			0.929	0.5231			0.941	0.3998
			0.3			0.927	0.5203			0.933	0.3990
		0.01	0.1			0.953	0.4716			0.935	0.4333
			0.2			0.935	0.5268			0.942	0.3986
			0.3			0.954	0.5232			0.932	0.3895
		0.05	0.1			0.928	0.6950			0.916	0.5066
			0.2			0.927	0.6117			0.928	0.4700
			0.3			0.911	0.6203			0.929	0.4684
		0.1	0.2			0.916	0.7439			0.898	0.5891
			0.3			0.883	0.7348			0.902	0.5883

Table (A.9) The coverage probabilities and mean lengths of the 95% confidence interval for the Partial Youden's index J_{p_1,p_2}.

σ	J	p_1	p_2	n	m	cp	al	n	m	cp	al
0.5	0.4	0	0.1	15	15	0.953	0.6082	30	15	0.940	0.5737
			0.2			0.965	0.6702			0.956	0.6299
			0.3			0.959	0.6403			0.953	0.4866
		0.01	0.1			0.958	0.6031			0.957	0.5814
			0.2			0.957	0.6635			0.957	0.6296
			0.3			0.967	0.6441			0.961	0.5970
		0.05	0.1			0.948	0.6108			0.956	0.5747
			0.2			0.967	0.6702			0.956	0.6332
			0.3			0.952	0.6333			0.962	0.5964
		0.1	0.2			0.961	0.6665			0.956	0.6271
			0.3			0.967	0.6366			0.960	0.5968
		0	0.1	30	30	0.944	0.4712	50	50	0.961	0.3787
			0.2			0.944	0.5110			0.955	0.4101
			0.3			0.958	0.4623			0.943	0.3621
		0.01	0.1			0.960	0.4681			0.946	0.3781
			0.2			0.943	0.5071			0.964	0.4100
			0.3			0.965	0.4609			0.946	0.3584
		0.05	0.1			0.952	0.4627			0.952	0.3786
			0.2			0.940	0.5102			0.962	0.4107
			0.3			0.954	0.4632			0.948	0.3603
		0.1	0.2			0.958	0.5098			0.952	0.4074
			0.3			0.950	0.4581			0.958	0.3619

Table (A.10) The coverage probabilities and mean lengths of the 95% confidence interval for the Partial Youden's index J_{p_1,p_2}.(continued)

σ	J	p_1	p_2	n	m	cp	al	n	m	cp	al
0.5	0.6	0	0.1	15	15	0.956	0.7163	30	15	0.959	0.6882
			0.2			0.972	0.6179			0.957	0.5732
			0.3			0.958	0.5297			0.947	0.5881
		0.01	0.1			0.956	0.7119			0.946	0.6802
			0.2			0.960	0.6129			0.961	0.5736
			0.3			0.962	0.5330			0.953	0.4881
		0.05	0.1			0.969	0.7196			0.958	0.6921
			0.2			0.960	0.6154			0.954	0.5784
			0.3			0.961	0.5298			0.967	0.4808
		0.1	0.2			0.959	0.6106			0.950	0.5690
			0.3			0.970	0.5282			0.965	0.4899
		0	0.1	30	30	0.946	0.5537	50	50	0.946	0.4462
			0.2			0.959	0.4303			0.951	0.3296
			0.3			0.956	0.3547			0.968	0.2660
		0.01	0.1			0.942	0.5539			0.946	0.4440
			0.2			0.948	0.4295			0.955	0.3292
			0.3			0.961	0.3579			0.937	0.2641
		0.05	0.1			0.948	0.5555			0.957	0.4491
			0.2			0.950	0.4309			0.958	0.3283
			0.3			0.959	0.3556			0.942	0.2653
		0.1	0.2			0.948	0.4313			0.950	0.3315
			0.3			0.953	0.3562			0.946	0.2646

Table (A.11) The coverage probabilities and mean lengths of the 95% confidence interval for the Partial Youden's index J_{p_1,p_2}.(continued)

σ	J	p_1	p_2	n	m	cp	al	n	m	cp	al
0.5	0.8	0	0.1	15	15	0.958	0.5628	30	15	0.964	0.5563
			0.2			0.957	0.4029			0.974	0.3661
			0.3			0.958	0.3579				
		0.01	0.1			0.965	0.5613			0.960	0.3624
			0.2			0.962	0.4040			0.957	0.3674
			0.3			0.959	0.3633			0.953	0.3224
		0.05	0.1			0.970	0.5443			0.965	0.5274
			0.2			0.964	0.3979			0.968	0.3661
			0.3			0.966	0.3547			0.953	0.3143
		0.1	0.2			0.969	0.3519			0.955	0.3309
			0.3			0.961	0.3220			0.967	0.2878
		0	0.1	30	30	0.957	0.3701	50	50	0.949	0.2657
			0.2			0.953	0.2525			0.943	0.1877
			0.3			0.959	0.2426			0.948	0.1858
		0.01	0.1			0.	0.			0.948	0.2628
			0.2			0.956	0.2538			0.951	0.1905
			0.3			0.952	0.2413			0.944	0.1865
		0.05	0.1			0.964	0.3633			0.955	0.2648
			0.2			0.960	0.2539			0.944	0.1891
			0.3			0.962	0.2385			0.940	0.1852
		0.1	0.2			0.965	0.2345			0.957	0.1774
			0.3			0.965	0.2216			0.957	0.1734

Table (A.12) The coverage probabilities and mean lengths of the 95% confidence interval for the Partial Youden's index J_{p_1,p_2}.(continued)

σ	J	p_1	p_2	n	m	cp	al	n	m	cp	al
0.5	0.9	0	0.1	15	15	0.960	0.3454	30	15	0.962	0.3177
			0.2			0.977	0.2574			0.954	0.2291
			0.3			0.958	0.2571			0.	
		0.01	0.1			0.973	0.3390			0.960	0.1934
			0.2			0.963	0.2661			0.963	0.2252
			0.3			0.969	0.2526			0.965	0.2223
		0.05	0.1			0.970	0.3209			0.958	0.2951
			0.2			0.953	0.2332			0.963	0.2067
			0.3			0.959	0.2190			0.957	0.1992
		0.1	0.2			0.967	0.1873			0.954	0.1664
			0.3			0.964	0.1789			0.950	0.1525
		0	0.1	30	30	0.963	0.4706	50	50	0.951	0.1366
			0.2			0.964	0.3602			0.966	0.1274
			0.3			0.953	0.2994			0.961	0.1275
		0.01	0.1			0.	0.			0.953	0.1367
			0.2			0.956	0.3601			0.939	0.1280
			0.3			0.969	0.2963			0.946	0.1268
		0.05	0.1			0.954	0.4751			0.950	0.1234
			0.2			0.962	0.3569			0.955	0.1167
			0.3			0.959	0.2953			0.949	0.1173
		0.1	0.2			0.	0.			0.951	0.0782
			0.3			0.955	0.1101			0.956	0.0774

Table (A.13) The coverage probabilities and mean lengths of the 95% confidence interval for the optimal cut-off points c_{po}.

σ	J	p_1	p_2	n	m	cp	al	n	m	cp	al
0.5	0.4	0	0.1	15	15	0.961	1.6068	30	15	0.939	1.5352
			0.2			0.957	1.3817			0.959	1.2972
			0.3			0.941	1.1980			0.943	0.8269
		0.01	0.1			0.961	1.5411			0.962	1.5253
			0.2			0.957	1.2946			0.963	1.2750
			0.3			0.949	1.1073			0.949	1.0614
		0.05	0.1			0.960	1.5212			0.965	1.5213
			0.2			0.973	1.2801			0.959	1.2601
			0.3			0.955	1.0701			0.945	1.0561
		0.1	0.2			0.958	1.2628			0.961	1.2576
			0.3			0.956	1.0578			0.951	1.0520
		0	0.1	30	30	0.942	1.0147	50	50	0.958	0.7719
			0.2			0.954	0.8723			0.944	0.6620
			0.3			0.948	0.7365			0.955	0.5715
		0.01	0.1			0.959	1.0240			0.947	0.7702
			0.2			0.952	0.8615			0.956	0.6642
			0.3			0.948	0.7329			0.945	0.5645
		0.05	0.1			0.942	1.0181			0.953	0.7718
			0.2			0.948	0.8701			0.957	0.6620
			0.3			0.952	0.7336			0.939	0.5693
		0.1	0.2			0.949	0.8598			0.944	0.6594
			0.3			0.949	0.7205			0.953	0.5702

Table (A.14) The coverage probabilities and mean lengths of the 95% confidence interval for the optimal cut-off points c_{po}.(continued)

σ	J	p_1	p_2	n	m	cp	al	n	m	cp	al
0.5	0.6	0	0.1	15	15	0.965	1.4985	30	15	0.955	1.5026
			0.2			0.963	1.1326			0.972	1.1001
			0.3			0.941	0.9025			0.944	1.0941
		0.01	0.1			0.959	1.4953			0.948	1.4718
			0.2			0.973	1.1275			0.967	1.1103
			0.3			0.931	0.9051			0.946	0.8279
		0.05	0.1			0.950	1.4930			0.951	1.5071
			0.2			0.955	1.1445			0.958	1.1267
			0.3			0.941	0.9019			0.949	1.0561
		0.1	0.2			0.961	1.1548			0.958	1.1318
			0.3			0.950	0.9122			0.943	0.8473
		0	0.1	30	30	0.955	1.0133	50	50	0.945	0.7720
			0.2			0.966	0.7692			0.952	0.6012
			0.3			0.939	0.5689			0.948	0.4182
		0.01	0.1			0.953	1.0159			0.947	0.7655
			0.2			0.962	0.7675			0.972	0.6023
			0.3			0.945	0.5779			0.936	0.4174
		0.05	0.1			0.956	1.0125			0.951	0.7747
			0.2			0.959	0.7726			0.961	0.5982
			0.3			0.931	0.5744			0.947	0.4174
		0.1	0.2			0.968	0.7782			0.964	0.6018
			0.3			0.945	0.5782			0.952	0.4155

Table (A.15) The coverage probabilities and mean lengths of the 95% confidence interval for the optimal cut-off points c_{po}.(continued)

σ	J	p_1	p_2	n	m	cp	al	n	m	cp	al
0.5	0.8	0	0.1	15	15	0.972	1.3376	30	15	0.965	1.3482
			0.2			0.969	0.9571			0.972	0.8481
			0.3			0.971	0.8446			0.	0.4086
		0.01	0.1			0.971	1.3334			0.971	0.8806
			0.2			0.980	0.9578			0.967	0.8559
			0.3			0.971	0.8436			0.963	0.6967
		0.05	0.1			0.968	1.3609			0.974	1.3684
			0.2			0.972	1.0050			0.974	0.9109
			0.3			0.966	0.8828			0.980	0.7429
		0.1	0.2			0.970	1.0918			0.970	1.0502
			0.3			0.968	0.9755			0.962	0.8958
		0	0.1	30	30	0.962	0.8917	50	50	0.968	0.6754
			0.2			0.974	0.5948			0.962	0.4317
			0.3			0.965	0.5510			0.961	0.4161
		0.01	0.1			0.	0.			0.953	0.6686
			0.2			0.972	0.5936			0.962	0.4337
			0.3			0.969	0.5470			0.961	0.4168
		0.05	0.1			0.968	0.8996			0.964	0.6797
			0.2			0.981	0.6072			0.965	0.4372
			0.3			0.965	0.5614			0.965	0.4203
		0.1	0.2			0.969	0.6816			0.965	0.4973
			0.3			0.950	0.6402			0.973	0.4800

Table (A.16) The coverage probabilities and mean lengths of the 95% confidence interval for the optimal cut-off points c_{po}.(continued)

σ	J	p_1	p_2	n	m	cp	al	n	m	cp	al
0.5	0.9	0	0.1	15	15	0.972	1.1752	30	15	0.970	1.0718
			0.2			0.975	0.9507			0.970	0.7939
			0.3			0.973	0.9242			0.9	0.
		0.01	0.1			0.981	1.1809			0.982	0.7294
			0.2			0.974	0.9673			0.978	0.8148
			0.3			0.983	0.9448			0.969	0.7797
		0.05	0.1			0.968	1.3517			0.960	1.3168
			0.2			0.969	1.1207			0.969	1.0391
			0.3			0.964	1.0916			0.972	0.9928
		0.1	0.2			0.956	1.2410			0.968	1.2126
			0.3			0.955	1.2034			0.957	1.1821
		0	0.1	30	30	0.973	0.7214	50	50	0.974	0.5221
			0.2			0.973	0.6246			0.978	0.4755
			0.3			0.976	0.6254			0.971	0.4757
		0.01	0.1			0.	0.			0.976	0.5228
			0.2			0.983	0.6293			0.974	0.4759
			0.3			0.974	0.6285			0.972	0.4756
		0.05	0.1			0.955	0.8382			0.962	0.6106
			0.2			0.969	0.7384			0.968	0.5614
			0.3			0.966	0.7339			0.971	0.5598
		0.1	0.2			0.9	0.			0.955	0.6991
			0.3			0.949	0.8773			0.950	0.6987