Statistical Evaluation of Diagnostic Tests

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Abstract--- *The use of routine laboratory tests in diagnosing disease is becoming of increasing importance. This emphasizes to test the efficiency of diagnostic tests, since relatively few diagnostic tests correctly classify all subjects tested as diseased or well. The more usual situation is one in which some well subjects are classified as diseased and some diseased subjects classified as well. In this type of situation, Diagnostics and prognostic models serve the purpose. Diagnostic models are usually used for classification and quite commonly used in medical field. In this paper, importance of statistical classification procedures are highlighted which helps in the evaluation of diagnostic tests.*

Keywords--- *Classification Procedures, Diagnostic Tests, Biomarkers, ROC Curve*

I. INTRODUCTION

IN the last two decades, the assessment of diagnostic tests has been rapidly increasing. A test procedure has been proposed for the evaluation of single diagnostic test and an extensive study and gave a test statistic for the comparison and evaluation of two diagnostic tests [10], [13]. An outline about the statistical treatment which helps in handling the problems with respect to one or more diagnostic procedures has been discussed [6]. Further an extensive review on the statistical techniques used for medical decision making, confining to the applications in diagnostic radiology [12]. Statistical Decision Making techniques in medicine are useful in determining the importance of the diagnostic tests, identification of threshold levels and so on. The primary function of a diagnostic test is to rule in or rule out disease, in turn which gives rise to the meaning that relatively few diagnostic tests correctly classify all individuals tested as diseased or well. The usual situation is one in which some well individuals are classified as diseased and some diseased individuals classified as well. To make a perfect decision making on the diagnostic tests there is a need to use advanced statistical techniques such as Decision Analysis, Regression Analysis, Cost-Effective Analysis, Logistic Regression, Receiver Operating Characteristic (ROC) curves, Discriminant Analysis and many more.

In this paper, importance of statistical classification procedures are highlighted, which helps in evaluating the diagnostic test, an attempt is also made to provide a discriminant score cutoff which enables to classify the new individual into one of the two groups. In the next section, we brief out the concepts of ROC curve analysis and Discriminant Analysis.

II. ROC CURVE AND ITS MEASURES

The ROC curve has its mathematical formulation which helps in fitting and estimating the parameters of the curve. The entire classification is carried out on the basis of a threshold value often referred to as Gold Standard, it determines the true condition status and also provides a source of information completely different from the tests under evaluation. The true condition status indicates the presence of disease otherwise absence. Two basic measures of ROC curves are sensitivity (Sn) and specificity (Sp).

Sensitivity refers to the ability of a test to detect the condition when it is present and Specificity refers to the ability of test to exclude the condition in patients without the condition.

An ROC curve is a plot of 1-Sp versus Sn. The construction of ROC curve primarily depends on the four possible states which are obtained on the basis of a threshold value i.e., TP, TN, FN and FP. The resulting curve is called empirical ROC [7]. Conventionally, it is assumed that diseased (D) and the healthy (H) individuals follow Normal distribution and hence the name Binormal ROC curve, with unknown monotonic transformation [1], [3]. Another important measure in ROC curve analysis is the Area Under the Curve (AUC), it is referred as the best index of discrimination [7], [8]. Basing on the AUC value the performance of a diagnostic test can be interpreted and it takes its range from 0.5 to 1.0. Higher the AUC values, the better will be the performance of a diagnostic test. If, for a test $AUC < 0.5$, one should not consider that test for further classification. A theoretical work has been proposed by combining the recent variable selection methods with AUC methods to optimize diagnostic accuracy of multiple risk factors [15]. The robustness of using the bi-normal model to fit the ROC curves [14]. A General linear model approach has been proposed for evaluating the ROC form and as well as estimating the AUC [11]. A linear regression frame work has been introduced to evaluate the ROC model by involving the covariate effects on the ROC curves [5].

III. PARAMETRIC FORM OF ROC CURVE

Let $D \sim N(\mu_D, \sigma_D^2)$ and $Y \sim N(\mu_H, \sigma_H^2)$, where D represents data from patients with disease and H represents data from those without disease. We can define false-positive and true-positive rates as

$$FP(c) = 1 - P(X > c) = 1 - \Phi\left[\frac{c - \mu_H}{\sigma_H}\right] = \Phi\left[\frac{\mu_H - c}{\sigma_H}\right] \quad (1)$$

and

$$TP(c) = P(X > c) = \Phi\left[\frac{(\mu_D - c)}{\sigma_D}\right] \quad (2)$$

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where c is the cutoff decision point and Φ is the cumulative normal distribution function.

The ROC curve can be traced out by the functions FP and TP as [4]

$$[FP(c), TP(c)] = \left\{ \Phi \left[\frac{\mu_H - c}{\sigma_H} \right], \Phi \left[\frac{\mu_D - c}{\sigma_D} \right] \right\} - \infty < c < \infty \quad (3)$$

The expression of area under the ROC curve is given as [3]

$$AUC = \Phi \left[\frac{a}{\sqrt{1+b^2}} \right] \quad (4)$$

here $a = \frac{\mu_D - \mu_H}{\sigma_D}$ and $b = \frac{\sigma_H}{\sigma_D}$.

IV. DISCRIMINANT ANALYSIS

Discriminant analysis is a technique where the discrimination is done by linear composites. A function that separates objects may sometimes serve as an allocator and one that allocates objects may sometimes act as discriminator. Using this technique, the discrimination function can be obtained which helps in classification of new individuals or objects into one of the groups. This technique helps in identifying the group centroids of various groups considered using which a cutoff can be obtained.

Let X_i ($i = 1, 2, \dots, m$) be the variable from $Np(\mu_i, \Sigma_i)$ with n_i samples each. Assume that $\Sigma_1 = \Sigma_2 = \Sigma_3 = \dots = \Sigma_m$. The optimality of classification depends on the assumptions of data which are

1. The predictor variables follow multivariate normal distribution.
2. The covariance matrices of different groups of data are homogeneous.

The discriminant function is nothing but a linear combination of the variables in the study. It is given as

$$D = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \dots + \beta_m x_m \quad (5)$$

where D is the discriminant score. This score is used to evaluate the function and evaluation is done using probabilities. The value of D is found out from the above expression by substituting the sample points in it. Thus, a set of n discriminant scores can be obtained. The correlation between the D values and x_j values can be computed which explains the measure of contribution of the j^{th} variable in discriminating the groups. However, we cannot obtain fruitful information if x_j and x_1 ($j \neq 1$) are highly correlated with each other.

Let the populations under study be denoted as Π_1 and Π_2 . The classification rule can be made functional and the object is placed under Π_1 [2] if

$$[(\bar{X}_1 - \bar{X}_2)' S_{pooled}^{-1}] x - \frac{1}{2} (\bar{X}_1 + \bar{X}_2)' S_{pooled}^{-1} (\bar{X}_1 + \bar{X}_2) \geq \ln \left[\left(\frac{c(1|2)}{c(2|1)} \right) \left(\frac{p_2}{p_1} \right) \right] \quad (6)$$

otherwise the object is assigned to Π_2 . Here $\bar{X}_1$ and $\bar{X}_2$ are unbiased estimates of μ_1 and μ_2 , respectively and S_{pooled} is the unbiased estimate of Σ . $c(1|2)$ and $c(2|1)$ are the costs of misclassification. p_1 and p_2 are prior probabilities of Π_1 and

Π_2 respectively. Here the x value is the new observation which has to be classified into one of the groups.

V. RESULTS AND DISCUSSIONS

Since the ADA values are normally distributed in both Healthy and Diseased groups, it is likely that the Binormal ROC produces more accurate AUC.

The fitted ROC model is found to be $ROC = \Phi(z)$, where $z = 6.5483 + 3.0546 * \Phi^{-1}(1 - Sp)$.

It means that the Sn value is the cumulative standard normal probability corresponding to z . The linear function z is a measure of discriminating ability of the marker. The intercept estimates the standardized gap between the means of the two groups while the slope estimates the scale with which z increases.

The AUC is estimated as 0.9792. This is lower than the AUC found from the non-parametric method which gave AUC = 1.00. One possible reason for this is that the data in each group contained some extreme values which have influenced the parameters a and b of the Binormal model.

The outliers are removed and the entire calculations are performed again. The following section shows the comparative details of the results.

i. Modified Results when Outliers are removed

When the outliers are removed the data set is left out with $n_1 = 23$ cases in H-group and $n_2 = 57$ cases in D-group. The following results provide a comparison between the two data sets, with outliers and without outliers.

S. No	Characteristics	With Outliers	Without Outliers
1	n_1	33	23
2	n_2	67	57
3	<ul style="list-style-type: none"> K-S Test: H Group K-S Test: D Group 	Z = 0.824; p-value = 0.506 Z = 0.669; p-value = 0.763	Z = 0.694; p-value = 0.721 Z = 0.601; p-value = 0.863
4	Trimmed Mean	H-Group: 20.61 D-Group: 74.51	H-Group: 20.56 D-Group: 73.97
5	<ul style="list-style-type: none"> AUC : Nonparametric AUC: Binormal 	1.00 0.979	1.00 0.997
6	<ul style="list-style-type: none"> Mean $\pm$ S.D for H Group Mean $\pm$ S.D for D Group 	20.48 $\pm$ 8.519 76.27 $\pm$ 26.022	20.65 $\pm$ 6.678 74.07 $\pm$ 18.086
7	Optimal Cutoff	36 IU/L	36 IU/L
8	S_n	1.00 (100%)	1.00 (100%)
9	(1- S_p)	0.00 (0.00%)	0.00 (0.00%)
10	Binomial Parameters	a = 6.5483; b = 3.0546	a = 7.9986; b = 2.7081

It can be observed that removal of the outliers has resulted in higher AUC in case of Binormal ROC, while there is no change in the nonparametric AUC. The Binormal model had a better fit when outliers are removed. The standardized

difference between means of diseased and healthy groups is measured by the parameter 'a', where as 'b' indicates the standard deviation of diseased group relative to healthy group. By removing the outliers the mean distance between populations is better identified when compared to the case with outliers. Again, removal of outliers has lead to lower relative standard deviation.

The Binormal ROC curve with and without outliers is shown in Figure 1

Figure 1: Binormal ROC Curves with and Without Outliers

It can be seen that, when the outliers are removed the ROC curve shows better shape.

ii. Effect of Age and Sex as Cofactors

The effect of cofactors like age and sex along with ADA can be brought into a Linear Discriminant Function (LDF) frame work so that a new patient subject with unknown group membership can be classified into TB / Non-TB group with a reasonable level of accuracy.

Using the data (Outliers removed) the following LDF is obtained with all variables included in the model (Enter Method).

$$D_i = -3.081 + 0.062 * ADA - 0.023 * AGE + 0.433 * SEX \quad (7)$$

where D_i is the discriminant score for the i th subject.

When this function is evaluated at the group means of the explanatory variables, we get the following scores.

Group	Function score at the centroids (means)
TB group	1.040
Non TB group	-2.577
Average (cutoff)	-0.7685

Now for the i th subject we evaluate the discriminant scores D_i using (7). If $D_i \leq -0.7685$, classify the subject as Non-TB otherwise classify as TB. These discriminant scores and the group membership are saved in the SPSS file as new variables. Since the actual scores are also known, the discriminating ability of the LDF is given by the confusion matrix which gives the percentage of correct classifications. This LDF correctly classifies 97.5 % of the subjects. The following graph shows the ROC curve when the LDF given in (7) is used as a classifier. The AUC is found to be 0.9589.

Figure 2: ROC Curve with all COVARIATES

Suppose AGE and SEX are not included in the model, then the discriminant function becomes

$$D = -3.733 + 0.064 * ADA$$

The cutoff score for discrimination is -0.722 and the following table of misclassification is observed. This method has given 96.3 % of correct classification.

iii. Stepwise Method of Estimating the LDF

Suppose LDF is estimated using stepwise regression instead of full regression, then the most important variables alone will be in the model and we get the following results.

- Stepwise Linear Discriminant Function

$$D_i = -2.935 + 0.063 * ADA_i - 0.020 * AGE_i \quad (8)$$
- Function value at the group centroids and the cutoff

Group	Function score at the centroids (means)
TB group	1.019
Non TB group	-2.525
Average (cutoff)	-0.753

- It is observed that this LDF correctly classifies 98.8 % of the subjects.
- The ROC curve for this LDF is shown in Figure (3)
- The AUC of this LDF is 1.00
- The Distribution of discriminant scores in each of the two groups is shown in Figure (4)

Figure 3: ROC Curve with Selected Covariates

Figure 4: Distribution of Discriminant Scores in the TB and Non-TB Groups

It can be seen that the stepwise linear discriminant function offers a better classification of subjects into correct groups using pleural ADA and AGE as the determinants of TB status.

This result helps in the screening of patients with unknown TB status. The ROC curve of the stepwise LDF has an AUC = 1.00, which means nearly 100% correct classification is done. The percentage of correct classification with different methods is shown below.

Method	Cases Correctly Classified
Full regression with ADA	96.3%
Full regression with ADA, AGE and SEX	97.5%
Stepwise regression with ADA, AGE	98.8%

It is also observed that the percentage of correct classification has increased with different discriminant functions.

VI. CONCLUSIONS

In this paper, focus was made on highlighting the importance of diagnostic test and the implications of statistical

techniques in evaluating the diagnostic tests. ROC curve analysis has been carried out to identify the model and the accuracy measure for a diagnostic test. Further, different discriminant functions were identified with various cofactor combinations. For each cofactor combination, discriminant function and discriminant scores were obtained. The average value of discriminant scores of healthy and diseased groups was considered as optimal cutoff point. Further, this discriminant score cutoff can be used to classify a new individual into one of the two known groups. It is proposed that for further classification the discriminant score cutoff can be used instead of clinical cutoff.

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