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Original Article

Statistical Considerations in Combining Multiple Biomarkers for Diagnostic Classification: Logistic Regression Risk Score Versus Discriminant Function Score

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ABSTRACT

Introduction: In clinical practices, multiple biomarkers are frequently used on the same subjects for the diagnosis of an adverse outcome. This study compares two alternative multiple linear regression approaches as the logistic regression model and the discriminant function score in combing several markers.
Methods: Ten thousand simulated data sets were generated from binormal and non-binormal pairs of distributions with different sample sizes and correlation structures. Each dataset underwent a logistic regression and the discriminant analysis simultaneously. The ROC analysis was performed with each marker alone and also their combining scores. For two alternative approaches, the average of AUC and its root mean square error (RMSE) were estimated over 10000 replications trials for all configurations and sample sizes used. The practical utility of the two methods is further illustrated with a clinical example of real data as well.
Results: The two approaches yielded identical accuracy in particular with binormal data. With non- binormal data, the logistic regression risk score produced an equal or slightly better accuracy than the discriminate function score.
Conclusion: Overall, the two approaches yield rather identical results. However, adopting the logistic regression model may incorporate a slightly better accuracy index than discriminant analysis with non-binormal data.

Introduction

Biomarkers provide a potential useful information in understanding the disease spectrum for purpose of screening, diagnosis, prognosis and monitoring the effect of therapeutic agents on the process of diseases. Receiver operator characteristic (ROC) analysis is a method of choice in the assessment of quantitative biomarkers in predicting the true state of diseased versus non-diseased.[1-3] The ROC curve shows the trade-off sensitivity

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versus 1-specificity as one changes the threshold of positivity and it is a proper method to determine the optimal cut-off for quantitative tests.[4] The area under the curve has a meaningful interpretation as a diagnostic accuracy of the test[5] and several methods of parametric and nonparametric have been developed to estimate its standard error.[6] However, several biomarkers are frequently ordered simultaneously on the same subjects by clinician, in particular, the diagnosis of malignancies. The conventional analysis uses each biomarker once at a time to derive the relevant ROC curve and its diagnostic accuracy to predict malignancies and compare the different biomarkers and to which has the most accuracy. However, each of these biomarkers may convey some independent information for detection of abnormality. Thus, for optimization of ROC curve, it is ideal to combine information of biomarkers in a single score.[7-10]

Several motivation examples have been illustrated in the literature for the rationale of combining biomarkers.[10-16] For example, sepsis remained a potential leading cause of death and more than 170 biomarkers for sepsis have been identified as useful markers including C-reactive protein, procalcitonin, different cytokines such as TNF-α, Il-1β, and IL-6 and other inflammatory cytokines and cell surface markers but no novel single maker can properly evaluate the monitoring treatment response for sepsis.[11] In some studies, combining biomarkers showed better accuracy in treatment monitoring response of sepsis with multiple cytokines than single biomarkers.[12-14] Because the sepsis is a disease with multiple immune responses, biologically combining biomarkers can improve prognostic accuracy. As another example, about 42 biomarkers (Gene Expression markers) were investigated for early detection of breast cancer.[15] In this example, a combination of picking five out of 42 genes produced the maximum AUC using the method of support vector machine analysis. Thus, the best four five-marker panels were identified. In another clinical setting, multiple serum biomarkers in tumor diagnosis with different cancer site were studied and the joint combinations of seven biomarkers including CEA+ NSE+ CYFRA21-1 + CA-125 + Ferritin+CA-199+AFP yielded the highest sensitivity of 97.6% for respiratory system tumors and the least sensitivity (45.4%) for gynecological neoplasm.[16] This joint presence of seven biomarkers had a higher accuracy for all sites of cancers than any other possible combinations of less than seven biomarkers. Additionally, it was evaluated the accuracy of a combination of four markers for the detection of ovarian cancer by three different methods of combining diagnostic markers. The logistic regression score had the best performance than the discriminant analysis and K-nearest neighbor method.[17] From a biological and statistical perspective, combining biomarkers provides more information for classification purpose. However, which method of combination of biomarkers and what subset of panels of makers are the most informative in optimizing diagnostic accuracy have not been fully elucidated.

Although, several methods of combining biomarkers have been suggested. The two approaches of the linear combination of independent variables for classification purposes have been used widely in the statistical analysis.[18-21] The first uses the discriminate function score as a linear combination of covariates and the second uses the logistic regression model risk score. The theoretical properties of these two approaches

have been studied widely,[9, 10] however, the choice between them still matters of questions and the superiority of either of these methods were not well understood by the clinician for optimization of ROC curve. Particularly, the underlying data of biomarkers are not Gaussian but a mixture of Gaussian or skew distribution[22] that may happen widely in clinical practice. Although some other nonlinear combinations are possible and it might be efficient. The logistic regression model is a general linear model and the linearity is assumed using the logit link function. One can use any polynomial forms such as x^2, x^3 in any linear model and it still would be linear with respect to the parameters of coefficients that are defined. In this paper, we did not use the forms of x^2 and x^3 because of the possible collinearity in our regression model. We used two alternative approaches of analysis with a similar patterns of linearity assumption to be comparable and we would be able to determine which model has a better performance for diagnostic classification of multiple biomarkers with binormal and non-binormal data of pairs of distributions. Thus, we adapted and compared these two alternative methodologies using simulated numerical data from various configurations of binormal and non-binormal models and with an application of clinical data in combining information of multiple biomarkers for detecting the clinical abnormality.

Methods

Simulated data

In the first data sets, the three markers as independent random variables (X_1, X_2, and X_3) were assumed to follow binormal distributions depending on disease condition with different parameters. Without loss of generalizability, supposing non-diseased distribution follows a standard Gaussian and we deliberately changed the parameters of Gaussian distributions for diseased to achieve the different degrees of accuracy from low to moderately high. Thus, in the first simulated data set, the random numbers of X_1, X_2, and X_3 were generated from pairs of binormal model for the diseased and non-diseased. The second simulated data sets (so-called random number of X_4, X_5, and X_6) were produced from the pairs of standard Gaussian distribution for non-diseased and gamma distribution with scale parameter of 1 andandndom number of X_4, X_5, X_6) nsidered as significant levels.xes as defined by the area under the curve (AUC)it score for ecachs the different shape parameter of 1.5, 2 and 2.5 that produced the different degree of accuracy index from low to relative high. The third data sets of independent variables (X_7, X_8 and X_9) were generated from the pairs of gamma distributions with a scale parameter of 1 and different shape parameters for diseased whereas non-diseased distribution was from a gamma with both scale and shape parameters of 1 (i.e. exponential distribution). The shape parameter of diseased distribution was deliberately varied to produce the desired level of accuracy. Figure 1 shows the pairs of distributions where the data have been generated in different panels. In each configuration of pair of distributions, a random sample of three independent variables/markers were generated with sample size of 50/50, 100/100, and 200/200 for diseased and non-diseased group respectively. The R software of version 3.4 was used to generate the data from different pairs of distributions and analysis.

In the second step, the data were simulated with triple correlated markers with three different correlation coefficient values: low (rho = 0.20), moderate (rho=0.50) and high (rho=0.80). We

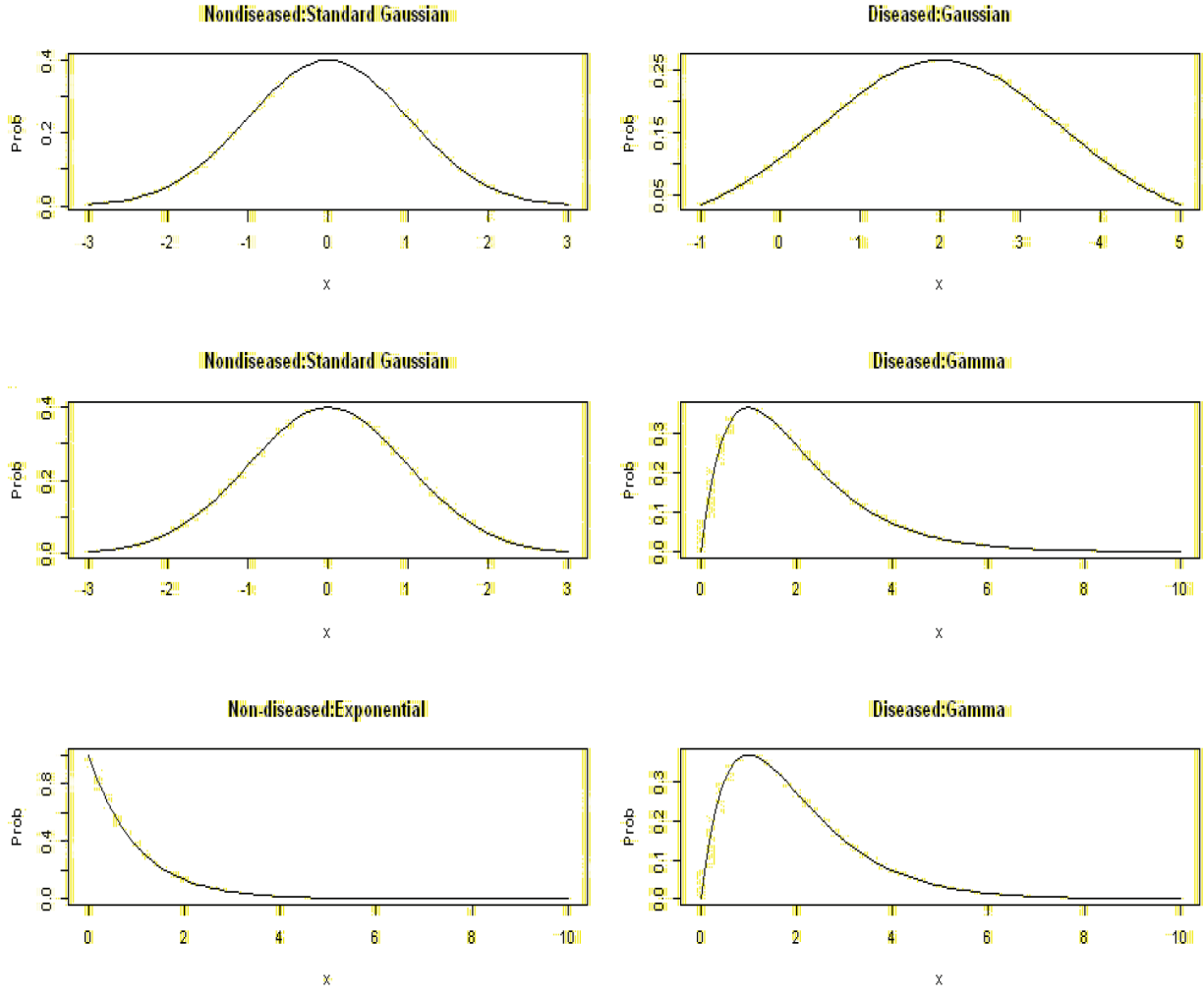

Figure 1. Configurations of pairs of distributions that the data have been generated (the parameters of diseased distribution have been changed deliberately to produce the different degree of accuracy).

have just constructed a 3 by 3 covariance matrix with a constant correlation coefficient and then multiplied the three independent vectors by Cholesky decomposition of that matrix to make them correlated. Thus, the triple correlated data were generated from different configurations of pair of distributions and different sample sizes similar to independent triple samples from diseased and non-diseased distributions.

Statistical analysis

In our analysis, the logit score as a linear combination of independent variables plus the discriminate scores were estimated for each data set separately. Each configuration of data sets and their combination predictive score from logit score and discriminant function score underwent to ROC analysis. The analysis was performed over 10000 trials. Each set of three decision variables in every three different configurations of distributions underwent two alternative analysis as logistic regression and discriminant analysis simultaneously. The average of AUC and the root mean square error (RMSE) for each marker alone and

their combinations of predictive scores from three sets of underlying pairs of distribution and sample sizes were computed over 10000 replications of trials.

The logistic regression model assumes a functional linear relationship between the log odds of probability of an adverse outcome with a set of explanatory variables such as $x_1, x_2 ... x_p$. This functional relationship is as follows:

$$logit\ (p) = \log\left(\frac{p}{1-p}\right) = \beta_1 x_1 + \beta_2 x_2 + \cdots + \beta_p x_p$$

The maximum likelihood method is used to estimate the regression coefficients that are interpreted as the log odds ratio of explanatory variables for an increment of x_i.

The discriminant analysis uses a linear function of explanatory variables of $x_1, x_2 ... x_p$ as

$$z=\beta_1 x_1 + \beta_2 x_2 + ... + \beta_p x_p$$

This function would discriminate between two groups of A and B if the mean value of z in two groups is reasonably far apart in comparison of the variation of z within groups. Thus, the estimation procedure of coefficients of a linear combination of markers tries to find the value of βs as

$$D^2 = \frac{(\bar{z}_A - \bar{z}_B)^2}{variance\ of\ z\ within\ group}$$

is as large as possible. The solution to this problem gives the regression coefficients as $(\bar{x}_A - \bar{x}_B)' S^{-1}$, where S is within group matrix of variance-covariance of data and $(\bar{x}_A - \bar{x}_B)$, is the estimate of between-group matrix. Similar to regression, the estimated coefficients can be calculated in standardized and unstandardized form but they are less informative than those in regression.

Results

Table 1 demonstrates the average of AUC and its RMSE over 10000 replication trials for various configuration and sample sized used with independent samples of the three makers. The results show that all X_1, X_2, and X_3 are predictors of disease and both logistic regression risk score and discriminant function score yielded a higher accuracy index than each individual marker. The logistic score of combining markers and discriminate function score produced a similar estimate of the accuracy index and its RMSE where the corresponding accuracy calculated by the AUC's was identical (AUC=0.858) with binormal data for all sample size used while as one expects the RMSE of AUC decreased as sample size increased. In Table 1, when data generated from a normal distribution for non-diseased and gamma distribution (skew to the right) for diseased, both methods of combined markers produced higher accuracy than individual markers alone but the logistic regression score (AUC=0.968 resulted to slightly superior accuracy than the discriminant score (AUC=0.966). for all sample size used. With non-binormal data (both pair members from gamma distribution), the two approaches of combined score results were rather a similar AUC and again both methods of combined markers yielded a greater accuracy index than individual markers. As an example of single trail, the derived ROC curve from logistic regression scores and discriminate analysis scores were shown in Figure 2 (panels of a, b and c). As this Figure shows in panel b, the logistic regression scores incorporated a bit higher accuracy than discriminant scores at a clinic relevant range of false positive fraction. Tables 2, 3, and 4 show the results of simulations with different configurations of pairs of distributions

Table 1. The average of AUC and the RMSE of each maker alone and their combinations using logit score and discriminant function score over 10000 simulated data sets generated from different configurations of pair of distributions according to sample size used with independent samples of markers.

Multiple markers	Pairs of Distributions	n = 50/50		n = 100/100		n = 200/200	
		AUC	RMSE	AUC	RMSE	AUC	RMSE
X_1	{Gaussian, Gaussian}	0.797	0.045	0.797	0.032	0.797	0.022
X_2		0.711	0.052	0.710	0.037	0.711	0.026
X_3		0.609	0.057	0.609	0.04	0.609	0.028
Logit score		0.858	0.038	0.854	0.027	0.852	0.019
Discriminant function score		0.858	0.038	0.854	0.027	0.852	0.019
X_4	{Gaussian, Gamma}	0.898	0.029	0.899	0.021	0.899	0.015
X_5		0.842	0.038	0.842	0.027	0.843	0.019
X_6		0.760	0.048	0.762	0.034	0.761	0.024
Logit score		0.968	0.014	0.967	0.011	0.967	0.007
Discriminant function score		0.966	0.014	0.966	0.011	0.966	0.007
X_7	{Exponential, Gamma}	0.647	0.055	0.646	0.039	0.646	0.027
X_8		0.751	0.049	0.751	0.034	0.75	0.024
X_9		0.823	0.041	0.823	0.029	0.823	0.021
Logit score		0.875	0.035	0.872	0.025	0.870	0.017
Discriminant function score		0.874	0.035	0.870	0.025	0.869	0.017

AUC area under the curve; RMSE Root Mean Square Error; AUC and RMSE are taken over 10,000 replications of the simulation and the numbers were rounded up to 3 digits

X_1˜ ND, N(0, 1); D, N(1.5, 1.5); X_2˜ ND, N(0, 1); D, N(1.0, 1.5); X_3˜ ND: N(0, 1); D, N(0.5, 1.5); X4˜ ND: N(0, 1); D, Gamma(scale=1, shape=2); X5˜ ND: N(0, 1); D, Gamma(scale=1, shape=1.5); X6˜ ND:N(0, 1); D, Gamma(scale=1, shape=1.0); X_7˜ ND, Gamma(scale=1, shape=1); D, Gamma(scale=1, shape=1.5); X_8˜ ND, Gamma(scale=1, shape=1); D, Gamma(scale=1, shape=2.0; X_9˜ ND, Gamma(scale=1, shape=1); D, Gamma(scale=1, shape=2.5).

Table 2. The average of AUC and the RMSE of each maker alone and their combinations using logit score and discriminant function score over 10000 simulated data sets generated from different configurations of pair of distributions according to sample size used with a low correlation structure between markers (rho=0.20)

Multiple markers	Pairs of Distributions	n = 50/50		n = 100/100		n = 200/200	
		AUC	RMSE	AUC	RMSE	AUC	RMSE
X_1	{Gaussian, Gaussian}	0.798	0.045	0.797	0.031	0.797	0.022
X_2		0.761	0.049	0.761	0.034	0.761	0.024
X_3		0.700	0.053	0.699	0.037	0.700	0.026
Logit score		0.858	0.038	0.853	0.027	0.852	0.019
Discriminant function score		0.858	0.038	0.853	0.027	0.852	0.019
X_4	{Gaussian, Gamma}	0.898	0.029	0.899	0.021	0.899	0.015
X_5		0.901	0.029	0.901	0.021	0.902	0.015
X_6		0.885	0.033	0.886	0.024	0.886	0.016
Logit score		0.968	0.014	0.967	0.010	0.967	0.007
Discriminant function score		0.966	0.014	0.966	0.010	0.966	0.007
X_7	{Exponential, Gamma}	0.647	0.055	0.645	0.039	0.646	0.027
X_8		0.765	0.047	0.764	0.033	0.765	0.024
X_9		0.853	0.037	0.853	0.027	0.853	0.019
Logit score		0.875	0.035	0.871	0.025	0.870	0.018
Discriminant function score		0.874	0.034	0.870	0.025	0.869	0.018

See footnote in Table 1.

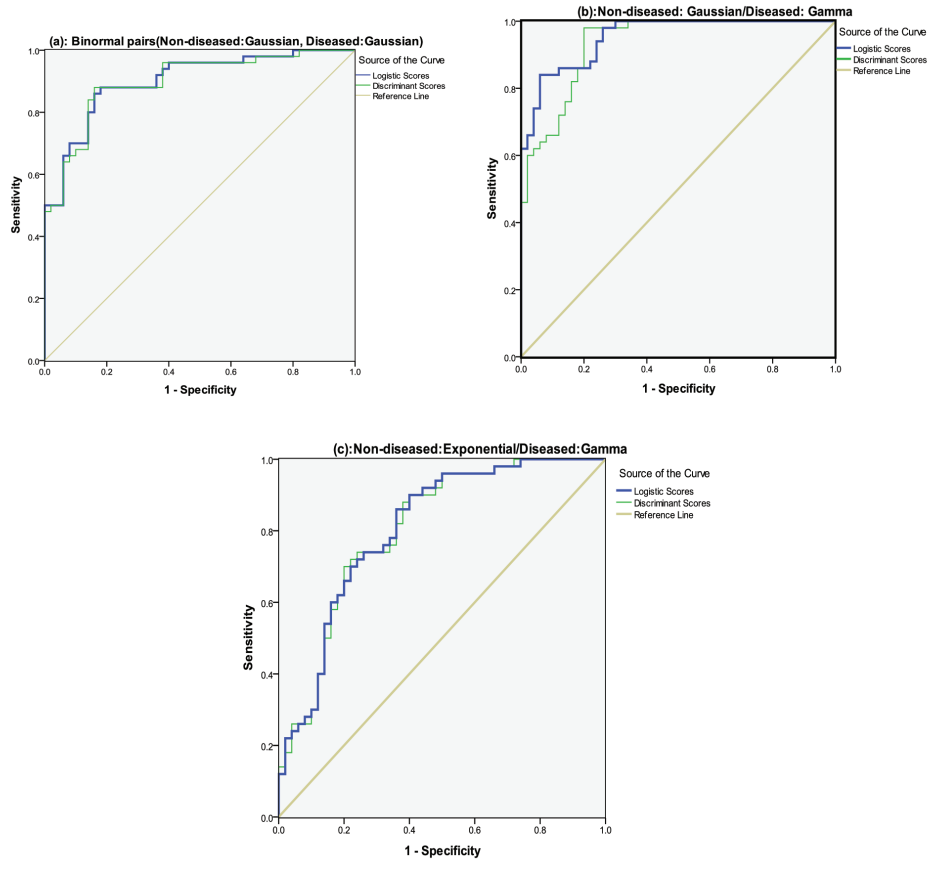

Figure 2. ROC curves derived from combined markers of logistic regression scores and discriminant scores of different configurations of pairs of distributions (panel (a): binormal; panel (b): only non-diseased: Gaussian and panel (c): both pair members: non-Gaussian)

when data of markers have a low, moderate and high correlation structure respectively. As one expects our results show that the AUC's from combined score with either comparative methods are higher than each marker alone with low correlation structure than high correlation. Even for a high correlation, the accuracies of combined scores of either method is improved but the additional gain in accuracies is small. The superiority of accuracy of combined logit score compared with discriminant function score was at level of third decimal place even with non- normal data and thus the difference of two comparative methods is almost negligible for clinical practices.

Illustration of methods with the clinical example

In a clinical study, 30 patients with inflammatory bowel disease (IBD) and 30 healthy controls were recruited.[23] The data of three biomarkers including erythrocyte sedimentation rate (ESR), malondialdehyde (MDA) and C-reactive protein (CRP) were measured simultaneously on each subject in both groups. In our analysis, first we graphically presented the distributions of these three biomarkers in patients and healthy controls separately (Figure 3) (panels of (a), (b) and (c)). The results in Figure 3 show that the distribution of CRP was rather skewed

Table 3. The average of AUC and the RMSE of each maker alone and their combinations using logit score and discriminant function score over 10000 simulated data sets generated from different configurations of pair of distributions according to sample size used with a moderate correlation structure between markers (rho=0.50).

Multiple markers	Pairs of Distributions	n = 50/50		n = 100/100		n = 200/200	
		AUC	RMSE	AUC	RMSE	AUC	RMSE
X_1	{Gaussian, Gaussian}	0.797	0.045	0.798	0.032	0.797	0.022
X_2		0.815	0.043	0.815	0.031	0.815	0.021
X_3		0.788	0.046	0.789	0.032	0.789	0.023
Logit score		0.858	0.038	0.855	0.027	0.852	0.019
Discriminant function score		0.858	0.038	0.854	0.027	0.852	0.019
X_4	{Gaussian, Gamma}	0.898	0.029	0.898	0.021	0.899	0.014
X_5		0.940	0.021	0.941	0.015	0. 941	0.011
X_6		0.946	0.020	0.946	0.014	0.947	0.010
Logit score		0.968	0.014	0.967	0.010	0.967	0.007
Discriminant function score		0.966	0.014	0.966	0.010	0.966	0.007
X_7	{Exponential, Gamma}	0.646	0.055	0.646	0.038	0.646	0.027
X_8		0.767	0.047	0.766	0.033	0.766	0.023
X_9		0.858	0.037	0.858	0.026	0.857	0.018
Logit score		0.876	0.035	0.872	0.025	0.870	0.017
Discriminant function score		0.874	0.035	0.870	0.025	0.869	0.017

See footnote in Table 1.

Table 4. The average of AUC and the RMSE of each maker alone and their combinations using logit score and discriminant function score over 10000 simulated data sets generated from different configurations of pair of distributions according to sample size used with a high correlation structure between markers (rho=0.80)

Multiple markers	Pairs of Distributions	n = 50/50		n = 100/100		n = 200/200	
		AUC	RMSE	AUC	RMSE	AUC	RMSE
X_1	{Gaussian, Gaussian}	0.797	0.045	0.798	0.032	0.798	0.022
X_2		0.841	0.040	0.841	0.028	0.841	0.020
X_3		0.832	0.041	0.833	0.029	0.832	0.020
Logit score		0.858	0.038	0.855	0.027	0.852	0.019
Discriminant function score		0.857	0.038	0.854	0.027	0.852	0.019
X_4	{Gaussian, Gamma}	0.898	0.029	0.899	0.021	0.899	0.014
X_5		0.950	0.019	0.951	0.013	0.951	0.009
X_6		0.957	0.017	0.958	0.012	0.958	0.008
Logit score		0.968	0.014	0.967	0.010	0.967	0.007
Discriminant function score		0.966	0.014	0.966	0.010	0.966	0.007
X_7	{Exponential, Gamma}	0.646	0.055	0.646	0.039	0. 647	0.027
X_8		0.749	0.049	0.749	0.034	0.749	0.024
X_9		0.830	0.041	0.829	0.029	0.829	0.020
Logit score		0.875	0.035	0.872	0.025	0.870	0.017
Discriminant function score		0.874	0.034	0.871	0.025	0.869	0.017

See footnote in Table 1.

in patients. We applied ROC analysis with logistic risk score and discriminate analysis scores when three continuous biomarkers were entered in both analyses. The findings of the ROC analysis of each biomarker alone and combined scores of both proposed methods were presented in Table 2 and Figure 4. The results show that the accuracy of combined scores is higher than each biomarker alone in both methods. As Figure 4 demonstrates, the logistic scores produced higher accuracy than discriminant scores in particular at a clinic relevant range of false positive fraction.

Table 5. The diagnostic accuracy of combined multiple biomarkers and each marker alone in prediction of inflammatory bowel disease as illustrated example

Test variables	AUC	SE	95% CI for AUC	P-value
Logit score	0.901	0.039	0.824–0.979	0.001
Discriminant score	0.857	0.048	0.763-0.951	0.001
CRP	0.832	0.052	0.731-0.933	0.001
MDA	0.776	0.060	0.658-0.893	0.001
ESR	0.653	0.071	0.514-0.792	0.041

ESR, Erythrocyte sedimentation rate; MD, Amalondialdehyde; CRP, C-reactive protein

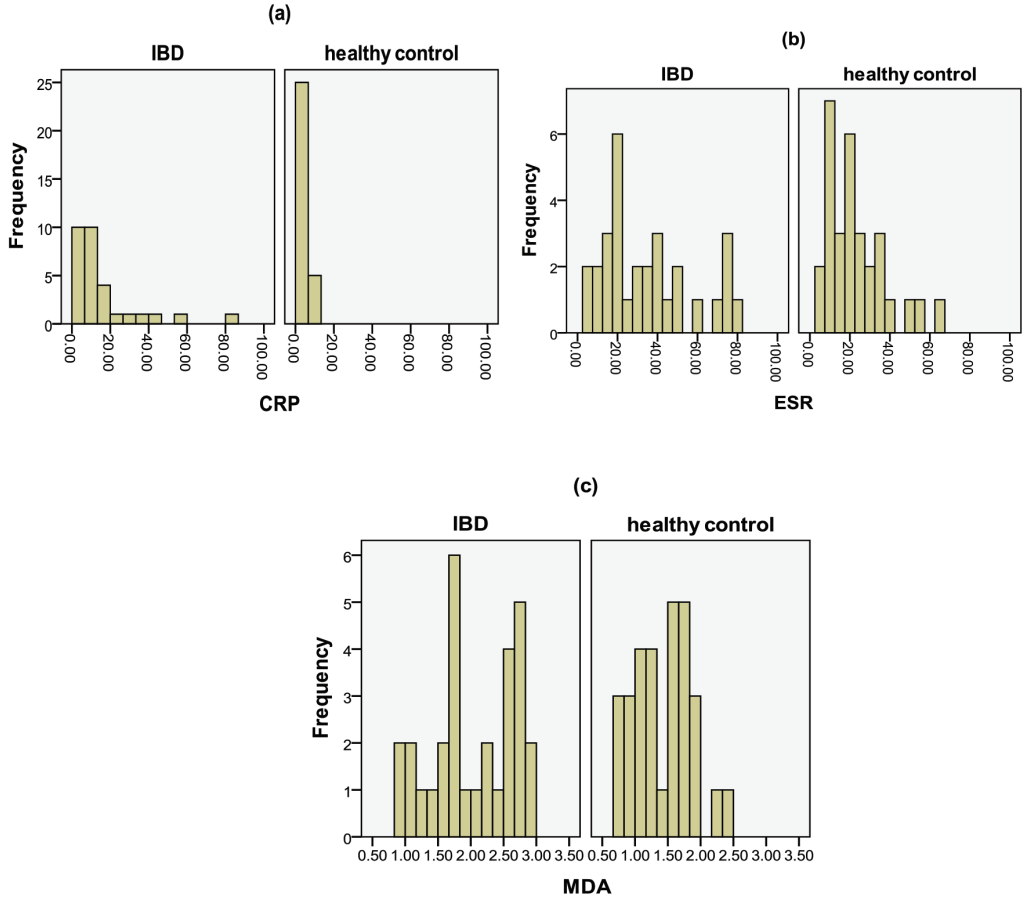

Figure 3. The distributions of three biomarkers in diseased and healthy control (panels of (a): CRP, (b): ESR and (c): MDA)

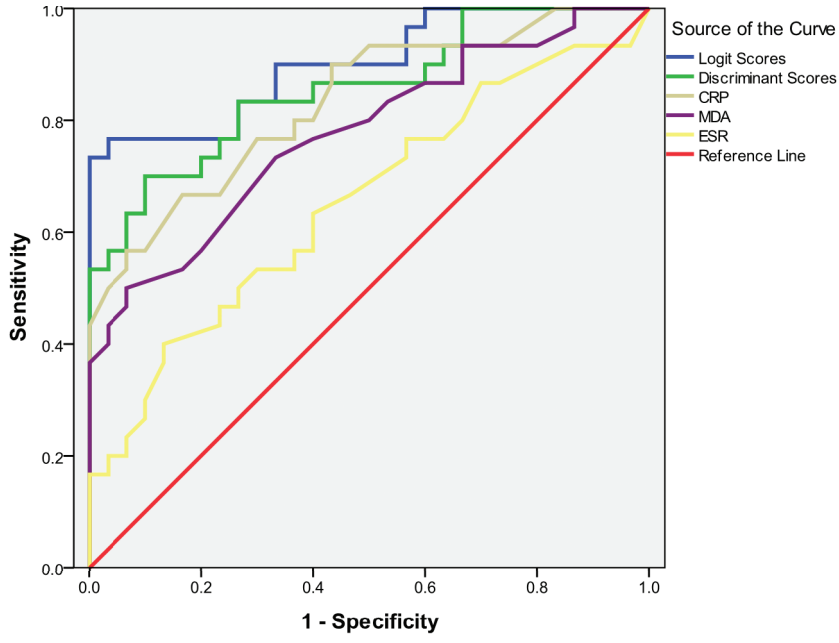

Figure 4. ROC curves of combined biomarkers by logistic regression scores, discriminant analysis scores and each biomarker alone in predicting IBD patients

Discussion

The results of our simulated data from various configurations of binormal and non-binormal pairs explored that the combinations of biomarkers enable to incorporate the independent information detected by multiple markers using multivariate statistical regression methods for assessment of diagnosis. In our simulated data, the two alternative approaches yield a similar AUC in particular with binormal data. While in some scenario of non-binormal pairs especially when only diseased distributions are non-Gaussian, the logistic regression model results may be slightly superior accuracy index than discriminant function score but the differences between two alternative methods are almost negligible. As one expects, the RMSE decreased as sample size increased in all scenarios of configurations studied and when the multiple markers are independent or either with a low correlation structure, the accuracy of combined scores are superior than those with highly correlated markers.

The discriminant analysis uses the multiple regression model has relatively stringent requirements on the distribution characteristic of data.[20] Although the assumption of multivariate normality of independent markers is required in the discriminant analysis in particular for testing of parameters our findings show this approach is rather robust for estimating regression parameters and discriminate scores. While the logistic regression is rather more ideal statistical model with no requirement on the distribution assumption of data in combining multiple markers since it is considered that the independent explanatory variables are as fixed covariates in the regression model.[24]

In our findings, the logistic regression model almost produces a combined score with equal or greater accuracy index than discriminate score. Because of the lack of any distributional assumption of data of markers in the logistic regression model, this feature makes the estimated regression coefficient of this

model to be more robust than conventional discriminant analysis. However, both logistic regression and discriminate analysis, the linearity assumption is inherent in the building of the regression model. In another condition with clinical data, combined score from a logistic regression model of two biomarkers in the diagnosis of nasopharyngeal carcinoma found that the sensitivity and specificity were both improved using the logistic regression than compared with those results of parallel testing and serial testing.[19] Some clinical studies with experimental data explored the incorporation of logistic regression model over the discriminant analysis in combining multiple biomarkers in the detection of ovarian cancer and other adverse outcomes as well.[17, 21, 25, 26] While in another clinical setting, discriminant function produced a proper valid and reliable constructed scoring system to identify the risk factors in distinguishing between healthy and ill neonates.[27] In addition, a few studies in clinical practice found similar findings in accuracy of combining multiple tests between logistic regression and discriminant analysis[20] but none of these studies in clinical research looked at the underlying distribution of data in combining biomarkers.

Another feature of the advantage of the logistic regression model in combining multiple biomarkers over the conventional discriminant analysis is that it allows incorporating the binary indicator of biomarkers in constructing and optimizing ROC curve while with a single binary biomarker, a reliable ROC curve cannot be derived. In some clinical investigation, using logistic regression model in combining multiple biomarkers, the prediction probability as a diagnostic indicator has been used in constructing ROC curve, instead we used the score of logit(odds) because of these two indexes are invariant in construction ROC curve. In the current study, we used the logit scale to construct the ROC curves instead of predicted probability. The ROC curve is invariant with the monotonic transformation of scale used to build it.[3] Since the transformation of logit (p)= log(p/(1-p)) is a monotonic where p is the predicted probability of developing disease. Thus, no matter one uses p or logit (p) in the construction of the ROC curve. However, the logit scale may be more attractive because of stretching scale from 0 to infinity and to adapt the linearity. For classification purpose, one might argue that the discriminate analysis is more proper than logistic regression analysis. The logistic regression model is a useful tool to assess the association, not classification. The classification and association models differ substantially in their clinical context and objectives.[28] But combining information of multiple markers by logistic regression, the logit scores, as risk scores, are applied to ROC analysis as a proper method of classification.

The best method of linear combination of biomarkers, which may not work properly when a strong nonlinearity exists in biomarker data. The proposed kernel-based AUC optimization method showed the superiority of this approach compared with other optimized combination methods when nonlinearity is present.[29] In addition, Yin and Tian developed an optimal linear combination method based on the Youden index that optimizes the total correct classification.[30] These two newly developed methods were not used in clinical assessment of multiple diagnostic tests by researchers perhaps because of the complexity of methods and the lack of availability of software.

Conclusion

The two alternative approaches yield the identical results in accuracy index. However, adopting the logistic regression model in multiple biomarkers assessment may incorporate a bit higher accuracy index and hence, it would produce an optimal cut-off with higher sensitivity and specificity for the diagnosis of any adverse outcome in clinical practices.

List of abbreviations

ROC, Receiver operator characteristic; AUC, Area under the curve; CI, Confidence interval; D, Diseased; ND, Non-diseased; N, Normal.

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Declarations

Ethics approval and consent to participate

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study has been approved by Ethical committee of Babol University of Medical Sciences.

Consent for publication

NA

Availability of data

The data is available from corresponding author with reasonable request.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

KH conceived the concept of this study and carried out the simulations and wrote the first draft of manuscript. ZG contributed the data generation and critically reviewed and made substantial contributions to the manuscript. VN also wrote the program in R codes for simulation and critically reviewed the paper. All authors approved the final manuscript.

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