Using ROC surface to predict preterm delivery based on hemoglobin level in the first trimester of pregnancy

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ABSTRACT

Receiver Operating Characteristics (ROC) curves have numerous applications for identifying a cut-off point in diagnostic tests. Nonetheless, given that sometimes two cut-off points have to be specified simultaneously, the ROC curve can be used to identify such points. The Volume under the ROC Surface (VUS) serves as a criterion for the accuracy of diagnostic tests. One of the unfortunate outcomes in pregnancy is pre-term delivery; it has been noted that an increase in the level of hemoglobin in the first trimester of pregnancy could result in preterm delivery in weeks 34 to 37 and that an ongoing hemoglobin increase could result in the delivery of a premature fetus before the 34th week of pregnancy. In this regard, in order to separate three groups of on-time delivery, pre-term delivery and immature delivery two cut-off points have to be identified, simultaneously. A suitable measure to identify such points is the ROC surface. In the current study, the hemoglobin information of the first trimester of pregnancy and delivery time of 623 pregnant ladies referring to Milad Hospital in Tehran in 2009-2010 was obtained. ROC surface was adopted to draw two ideal cut-off points for the first trimester of pregnancy. The optimal points for hemoglobin of the first trimester computed with the ROC surface were 12.54 and 13.2. While a hemoglobin rate less than 12.54 indicated an on-time delivery, a rate between the two cut-off points referred to pre-term delivery and hemoglobin more than 13.2 showed a premature fetus. The three-dimensional ROC surface is a useful tool that can visually summarize the ability of a biological marker to classify individuals between more than two groups.

Keywords: ROC surface; proper classification rate; time of delivery.

INTRODUCTION

Nowadays, biomarkers are increasingly adopted to diagnose diseases. Disease diagnosis depends on the association between the biomarker levels and condition of the disease, according to which biomarker levels are not similar in the healthy and sick individuals. With identification of cut-off points, biomarker level can be divided into two sections which could then serve as a criterion to distinguish between healthy and sick individuals. ROC curve is the commonest technique for measuring the validity of biomarkers, which is obtained by drawing the true positive rate (sensitivity) against the false positive rate (specificity) on all possible cut-off points.

Sometimes, with deterioration of the disease, the biomarker level would change by going up or dropping down and the degree of change could indicate the level of disease progress. In such conditions, the simultaneous identification of more cut-off points and classification of individuals into several groups is the main focus. In many occasions, the identification of two cut-off points and, accordingly, the classification of the individuals into three groups is planned for. One of the statistical methods that is used for simultaneous identification of two cut-off points is

the ROC surface. ROC surface is the generalization of ROC curve from a two-dimensional space into a three-dimensional one. The main objective of this article is the providing of ROC surface and its application in using biomarkers to diagnose diseases. In this article, this method has been used to predict time of delivery based on hemoglobin rate at the first trimester of pregnancy.

Preterm delivery is one of the disfavored consequences of pregnancy. Preterm delivery means delivery prior to completion of the 37th week of pregnancy, which is computed according to the last menstruation. Premature delivery of fetus happens when the child is born before 34 weeks [11]. Preterm delivery, following hereditary disorders, is the most common cause of newborn fatalities, with 5% incidence in developed countries and 25 % in developing countries [12]. The first step in predicting and preventing preterm delivery is the identification of women at risk. At the moment there is no proper, cheep and effective screening test with limited complications.

Todays, although specialist midwives do not consider a high level of hemoglobin the same as a low level, recent studies have spotted a link between high level of hemoglobin in pregnant mothers and its improper consequences such as preterm delivery [13]. Therefore, at this article, simultaneous identified two cut-off points, using ROC surface, can serve as a criterion for predicting preterm delivery.

MATERIALS AND METHODS

The data used in this study include the level of hemoglobin at the first trimester of pregnancy and the condition of preterm delivery of 623 pregnant women at their first trimester of pregnancy, referring to Milad Hospital in Tehran from 2009 to 2010. The level of hemoglobin in the first trimester of pregnancy was measured at the laboratory of Milad Hospital. The samples were then followed up until the delivery time.

Data Analysis

ROC curve is the commonest technique for assessing diagnostic tests which is used to identify a cut-off point. As such, the related biomarker will present a criterion for classification of healthy and sick individuals. Drawing the ROC curve would involve the identification of true positive values against false positive values on single squares in proportion to cut-off points. The Area Under ROC Curve (AUC) is a criterion for testing the accuracy of the diagnostic test. When the simultaneous identification of two cut-off points is needed, the ROC surface is used. ROC surface is the extension of ROC curve from a two-dimensional space to a three dimensional one, which makes it possible to properly predict the status of each special class (group) at a particular stage. As correct classification rates of the two groups, i.e. specificity and sensitivity are necessary to draw ROC curve, correct classification rates of the three groups are also essential to draw the ROC surface [2, 3]. For obtain the ROC surface, one just needs to draw correct classification rates for all possible pairs of cut-off points in unit cube. The ideal place would be the point on the depicted surface which is closer to the cube angle with 1, 1, 1 in size, and the cut-off pairs would be the intended points [4, 5]. Similar to the ROC curve, the ROC surface has a criterion for assessing the accuracy of diagnostic tests. The volume under the ROC Surface, shown by a symbol "VUS", is a criterion for measuring the validity of the diagnostic test. VUS is direct generalization of AUC, with an interpretation quite similar to it [6-8]. If, for example, the level of biomarker for the first group is less than the second group, and also the level of the biomarker in the second group is less than the third group, then VUS would be equal to the possibility that the mount of biomarkers obtained from three individuals selected randomly from groups 1, 2 and 3, have the expected order as well [5].

In order to find the best cut-off points and do the statistical analyses, we used "R" version 2-14-2, with DiagTest3Grp package and "Matlab" software. Along with drawing the ROC surface, two optimal cut-off points for hemoglobin of the first trimester of pregnancy were identified so that women with on-time delivery, preterm delivery or premature delivery could be separated from each

other. Hence, by comparing the level of hemoglobin of the first trimester of pregnancy with pre-identified cut-off points, the delivery time can be predicted.

RESULTS

Among 623 pregnant women under study, 540 (87 %) had on-time deliveries, 58 (9 %) had preterm deliveries and 25 (4 %) had premature fetus deliveries. Further description on the three groups in terms of level of hemoglobin at the first trimester of pregnancy appears in Table 1. A logistic ordinal regression was used to compare the mean hemoglobin level in three groups. There was a significant relation between the hemoglobin and time of delivery (P=0.01). One unit increasing in hemoglobin level results that the chance of preterm delivery increases by 30 %.

Table 1- comparing the mean hemoglobin level in the first trimester of pregnancy among three group s delivery.

Delivery position	Term (540 cases)	Preterm (58 cases)	Premature fetus (25 cases)	Logistic ordinal p-value
Hemoglobin mean(SD)	12.61 (0.04)	12.78 (0.18)	13.02 (0.189)	0.01

According to the ROC surface, the cut-off points for hemoglobin were 12.54 and 13.2. Therefore, hemoglobin level less than 12.54 would indicate on-time delivery, hemoglobin level between the two cut-off points would refer to preterm delivery and hemoglobin level more than 13.2 would indicate premature fetus delivery. ROC surface are shown pictorially in figure 1.
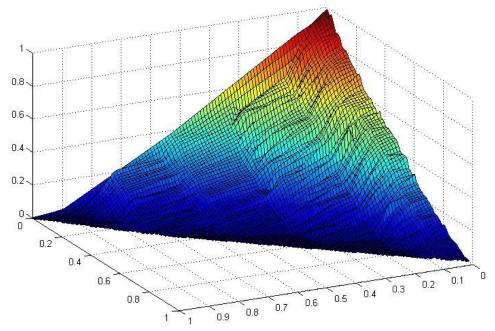

Figure 1- ROC surfaces corresponding to hemoglobin levels

Based on such cut-off points, true classification rates for on-time, preterm and premature deliveries were 47%, 22% and 48% in order. In other words, by comparing the level of hemoglobin at the first trimester of delivery with these cut-off points, the pregnancy status of 47% of mothers with on-time deliveries could be precisely predicted. Also, in the first three months of pregnancy, the delivery status of 22% of mothers with preterm deliveries could be correctly

predicted; furthermore, 48% of mothers with premature fetus deliveries can be accurately forecasted. Frequency of deliveries in three groups

of mothers with on-time, preterm and premature fetus deliveries, with pre-identified cut-off points using ROC surface, appear in Table 2.

Table 2 - Frequency of deliveries in three groups of mothers with on-time, preterm and premature fetus deliveries

Predictions	Real situation			Total
	Term **N (%)**	**Preterm** **N (%)**	**Premature fetus** **N (%)**	
Term	252 (47)	21 (36)	7 (28)	280
Preterm	131 (24)	13 (22)	6 (24)	150
Premature fetus	157 (29)	24 (41)	12 (48)	193
Total	540 (100)	58 (100)	25 (100)	623

The main diameter in table 2 shows the number of people that have been properly classified. For example, of 58 preterm deliveries and of 25 premature fetus deliveries, respectively 13 and 12 individuals were correctly predicted by the VUS method.

DISCUSSION

Recently, the ROC methodology by developing a three dimensional surface has been extended to the three-group diagnostic [2-5]. In the current article, ROC surface for identification of two cut-off points in three group classification was adopted. In this regard, so far different perspectives have evaluated the ROC surface. In 2005, Ameat used the ROC surface method to test the scanning system of Computer-Aided Diagnosis (CADx) in investigating the chest cancer; they additionally compared the ROC method with the other existing methods [14]. In 2006, Nakas used the ROC surface method for Methylation marker in order to histologically classify pulmonary carcinomas of their patients. Yabous in 2008 used ROC surface volume method together with NAA/Cr biomarker to predict brain damage in patients afflicted with AIDS [4].

Regarding the implementation of results, the study indicated that on-time delivery could be predicted for hemoglobin less than 12.54, preterm delivery can be expected for hemoglobin level between two cut-off points and premature fetus delivery

can be forecasted for hemoglobin level above 13.2.

In Safavi study in 2010, there was a significant difference in hemoglobin level between healthy individuals and those with preterm delivery (p=0.04); their study suggested 12.35 as a suitable cut-off point index for diagnosing preterm delivery. In their study hemoglobin test in the first trimester of pregnancy enjoyed 74% sensitivity and specificity of 38.4 was suggested for early diagnosis of preterm delivery [11].

In the study by Zhou in 1998, there was a significant link between high levels and low levels of hemoglobin at early pregnancy and preterm delivery, so that the relative risk of preterm delivery in pregnancies with hemoglobin level of 12-12.9 was 1.11, in those with level of 10-10.9 was 1.64, in those with level of 9-9.9 was 2.63 and in those with level of 6-8.9 was 3.73. Altogether, the study indicated that the risk for preterm delivery goes up as the level of hemoglobin increases [15].

In 1986, Murphy carried out an extensive study to investigate any possible relationship between hemoglobin level at the first referral and the last phase of pregnancy. The results indicated a link between preterm delivery and high level of hemoglobin, more than 13.3, and low level of hemoglobin, less than 10.4. Preterm delivery in women with high level of hemoglobin was more than those with normal hemoglobin [16].

The study of Phaloprakarn in 2008 and Scanlon in 2000 showed a significant relationship between high level of hemoglobin, at the first trimester of pregnancy, and preterm delivery [17, 18].

The studies referred in above, either investigated the link between high levels of hemoglobin and preterm delivery or identified a cut-off point as a criterion for prediction. The current study, however, adopted a different approach by simultaneously identifying two cut-off points in predicting preterm delivery and premature fetus delivery. However, the sample size in this study was not satisfactory because subjects in both preterm deliveries and premature fetus deliveries were fewer than expected. This limitation could have affected the results, particularly the true classification rates. Future studies with similar objectives but sufficient sample size for three types of deliveries are recommended. This could be done using the results or the present study as a pilot. Because there is no reference about sample size for three classes in ROC surface, It suggests that use the simulation for determine the sample size effect on the true rate classification.

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