Accommodating Maternal Age in CRIB Scale: Quantifying the Effect on the Classification

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Abstract. Receiver operating characteristic (ROC) curves are a well-accepted measure of accuracy of diagnostic tests using in continuous or ordinal markers. Based on the notion of using a threshold to classify subjects as positive (diseased) or negative (no diseased), a ROC curve is a plot of the true positive fraction (TPF) versus the false positive fraction (FPF)for all possible cut points. Thus, it describes the whole range of possible operating characteristic for the test and hence its inherent capacity for distinguish between two status. The clinical severity scale CRIB - Clinical Risk Index for Babies, emerged in 1993 to predict the mortality of newborn at less than 32 weeks of gestation and very low birth weight ($< 1500gr$) [4]. In previous work of Braga [3] this index was reported as showing a good performance in assessing risk of death for babies with very low birth weight (less than 1500 g weight). However, in some situations, the performance of the diagnostic test, the ROC curve itself and the Area Under the Curve(AUC) can be strongly influenced by the presence of covariates, whether continuous or categorical [5], [32], [33]. The World Health Organization and the Ministry of Health, defined as "late pregnancy" that thus occurs in women over 35 years. In this work, using the conditional ROC curve, we analyze the effect of one covariate, maternal age, on the ROC curve that representing the diagnostic test performance. We chose two age status, less than 35 years old and equal or greater than 35 years old, to verify the effects on the discriminating power of CRIB scale, in the process classification using R and STATA software.

Keywords: Conditional ROC (Receiver Operating Characteristic) curve, CRIB (Clinical Risk Index for Babies), maternal age, AUC (Area Under the Curve).

1   Introduction

The discriminatory capacity of a continuous marker or diagnostic test X, is usually measured by means of the receiver operating characteristic (ROC) curve [1] [2]. Under the conventional assumption that high marker values are indicative of disease, classification on the basis of X of an individual as healthy ($\bar{D}$) or diseased (D) can be made by the choice of a cut-off value c, such that, if $X \geq c$, the individual is classified as diseased, and if $X < c$, the individual is classified as healthy. Hence, for each cut-off value, c we define the true positive fraction,

$$TPF(c) = P[X \geq c|D] \tag{1}$$

and the false positive fraction,

$$FPF(c) = P[X \geq c|\bar{D}] \tag{2}$$

In such a situation, the ROC curve is defined as the set of all pairs for these fractions that can be obtained on the variation of cut-off value, c, $(TPF(c), FPF(c))$, $c \in (-\infty, +\infty)$, or, equivalently, as a function:

$$ROC(p) = S_D(S_{\bar{D}}^{-1}(p)), \text{for } p \in (0, 1) \tag{3}$$

where S_D and $S_{\bar{D}}$ denotes the survival functions of X in diseased and healthy subjects, respectively [29]. The Area Under the ROC Curve (AUC) is considered as an effective measure of inherent validity of a diagnostic test. This index is useful in evaluating the discriminatory ability of a test to correctly pick up diseased and non-diseased subjects and finding optimal cut-off point to least misclassify diseased and non-diseased subjects.

In many practical situations, however, a marker's discriminatory capacity may be affected by a set of continuous and/or categorical covariates.

1.1   Maternal Age as Covariate

Nowadays, fortunately, few women have a risky pregnancy. However, in cases where there is such a quiet evolution, because there is a chronic illness or because medical or pregnancy related problems arise during the nine months, it is essential a proper and timely monitoring. By definition, there is a high-risk pregnancy when the probability, of an adverse outcome for the mother and/or infant during or following pregnancy and delivery, is increased above the mean baseline risk in the general population by the presence of one or more risk factors. These factors can be divided into maternal and fetal. The maternal factors

include maternal age (less than 15 years and upper 35 years). Women over 35 years old are at greater risk of having a baby with chromosomal abnormalities. The existence of hypertension, diabetes and complications during labor is also more frequent. Below 15 years old, low birth weight and preeclampsia, may occur. There are many works in which the mother's age is the subject of study, either in association with low birth weight, either because it can be the cause of preterm birth [8], [30], [31]. Most research indicates that very young mothers imply an increased risk of low birth weight and premature births. Few studies have been conducted to older mothers, although this is the current trend in most developed societies. The few studies associate old maternal age to a potential decrease in babys development during pregnancy. Aras [9] presents several studies in which it is concluded that low birth weight depends not only on the age of the mother but also of health care during pregnancy, biological characteristics, race, socio-economic factors, weight gain during pregnancy, among others. Friede et al. [7], in a study to examine the effect of maternal age on low birth weight and infant mortality, used data from young mothers and found a strong association between young maternal age and infant mortality and also with a high prevalence of infants with low birth weight.

2   Empirical Estimators of the ROC Curve

There are many estimators proposed for the ROC curve when it is defined by the expression (3). Assuming that two independent samples, one from diseased population (D) and another from healthy $(\bar{D})$ are avaiable, we may obtain the empirical estimators of survival functions of X in diseased and healthy subjects, $\widehat{S}_D$ and $\widehat{S}_{\bar{D}}$, respectively. Thus we can write the empirical ROC curve estimator by the following expression:

$$\widehat{ROC}(p) = \widehat{S}_D(\widehat{S}_{\bar{D}}^{-1}(p)), \text{ for } p \in (0,1) \tag{4}$$

For each possible cut-off value c, the fractions of true positives and false positives are obtained by:

$$\widehat{TPF}(c) = \frac{1}{n_D} \sum_{i=1}^{n_D} I\left(X_{Di} \geq c\right) \tag{5}$$

and

$$\widehat{FPF}(c) = \frac{1}{n_{\bar{D}}} \sum_{i=1}^{n_{\bar{D}}} I\left(X_{\bar{D}i} \geq c\right) \tag{6}$$

Thus, the estimated ROC curve is obtained by representing pairs of values

$$(\widehat{TPF}(c), \widehat{FPF}(c)), c \in (-\infty, +\infty) \tag{7}$$

Similarly, the empirical estimators of survival function of X in diseased and healthy subjects presents in the expression for the ROC curve estimator (4) can be obtained by

$$\widehat{S}_D(c) = \frac{1}{n_D} \sum_{i=1}^{n_D} I\left(X_{Di} \geq c\right) \tag{8}$$

and

$$\widehat{S}_{\bar{D}}(c) = \frac{1}{n_{\bar{D}}} \sum_{i=1}^{n_{\bar{D}}} I\left(X_{\bar{D}i} \geq c\right) \tag{9}$$

One of the biggest advantages of using ROC curves is the possibility of comparing diagnostic tests, such in medical diagnosis, trough the AUCs obtained from these curves. In this study, we use the statistical approach to the Wilcoxon-Mann-Whitney test to calculate the estimate of AUC index, which summarize each ROC curve in terms of area bellow it. One possibility to test weather the difference between two ROC curves is statistically significant, involves the AUC index. Consider AUC_1 and AUC_2 the areas obtained from two ROC curves. The relevant hypothesis to test, H_0 is that the two data sets come from ROC curves with the same AUC:

$$H_0:\ \text{AUC}_2 - \text{AUC}_1 = 0\ \ \text{vs}\ \ H_1:\ \text{AUC}_2 - \text{AUC}_1 \neq 0$$

A method for testing the difference between the two areas for independent samples is based on critical ratio Z [25]:

$$Z = \frac{AUC_2 - AUC_1}{\sqrt{SE_{AUC_1}^2 + SE_{AUC_2}^2}} \sim N(0,1) \tag{10}$$

3   ROC Curve with Covariates

It is well known that a diagnostic test performance may be strongly influenced by covariates. In such situation, the ROC curve (and its summary indices, such as the area under the curve) may be underestimated if important covariates are neglected. In most studies, paralell to the diagnostic test used to classify individuals in D and $\bar{D}$ class, one or more covariates may be associated with the classification variable and can provide extra information about the individuals classification and increase the discriminating power of the curve. In such situations, the interest must be focused on assessing the discriminatory capacity of marker Xs regarding to the values assumed by the covariate that we represent by Y. The ROC curve in this case can be considered for each value of the covariate, y. Changes that occurs in curve, due to these values, might mean that

the covariate has effect on the discriminating power of the diagnostic test. If the conditional survival functions of X_D and $X_{\bar{D}}$, given Y, are denoted by S_{DY} and $S_{\bar{D}Y}$ respectively, the conditional ROC curve is defined as

$$ROC_y(p) = S_{DY}(S_{\bar{D}Y}^{-1}(p)), \text{for } p \in (0,1) \qquad (11)$$

The first works developed in the area of adjustment of covariates on the discrimination or classification of individuals into classes, are assigned to Cochran and Bliss [10], Cochran [11] and Rao [13]. These publications were focused on the selection of discriminating variables. The rules to adjust covariates requires the formulation of appropriate probability models and are developed later in works of Lachenbrush [12] and McLachlan [14]. However, these works focus on classification rules, providing only background of interest to the study. The first works on adjustment of covariates were from Guttman et al. [15] and Tolsteson and Begg [16]. The first authors, in the context of stress strength models, have obtained the ROC curve as a function of covariates by fitting linear regression models to X (diseased subjects) and Y (healthy subjects), assuming normality with different variances. The adjustment of ROC curves from continuous scales was studied by Smith and Thompson [17], Pepe [18], [19], [20], Faraggi [21], Janes and Pepe [22], [23] among others. The summary measures from ROC curves with adjustment of covariates was studied by Faraggi [21] and by Dodd and Pepe [24].

4   Covariate ROC Curve Adjustment

To assess the possible covariate effects on the ROC curve, two different approaches have been suggested in the statistical literature. The **Induced** methodology proposed by Tolsteson and Begg [16]; Zheng and Heagerty [26]; Faraggi [21], in which the covariates effect on diagnostic test is modeled in the two populations (D and $\bar{D}$) separately. The covariate effects on the associated ROC curve can then be computed by deriving the *induced* form of the ROC curve.

Otherwise the **Direct** method proposed by Pepe [20]; Alonzo and Pepe [28]; Cai [27], assumes a ROC curve with *direct* effect of the covariates on it.

4.1   Induced Adjustment

Suppose there is a set of covariates Y_D associated with the diseased population and a set of covariates $Y_{\bar{D}}$, associated with the healthy population. In many applications, some if not all covariates are common to both populations, but there is no need for two sets are identical. If α_D and $\alpha_{\bar{D}}$ are scalars, β_D and $\beta_{\bar{D}}$ are vectors of unknown parameters with Y_D and $Y_{\bar{D}}$ elements, then the average values associated with the diagnostic test for the diseased and healthy populations, for certain values of the covariates, can be modeled as [29]

$$\mu_D(Y_D) = \alpha_D + \beta_D^T Y_D \qquad (12)$$

and

$$\mu_{\bar{D}}(Y_{\bar{D}}) = \alpha_{\bar{D}} + \beta_{\bar{D}}^T Y_{\bar{D}} \tag{13}$$

The model specification is complete assuming that these average values are normally distributed with standard deviation σ_D and $\sigma_{\bar{D}}$, respectively. This model is essentially the binormal by specifying the population average. Then it follows that the equation of the ROC curve is given by

$$ROC_y(p) = \phi\left(\frac{\mu_D(Y_D) - \mu_{\bar{D}}(Y_{\bar{D}}) + \sigma_{\bar{D}}\phi^{-1}(p)}{\sigma_D}\right), p \in (0,1) \tag{14}$$

The least squares regression can be used to obtain point estimates of α_D, $\alpha_{\bar{D}}$, β_D and $\beta_{\bar{D}}$. Substituting these estimates in the above expression for certain y_D, $y_{\bar{D}}$ values of Y_D and $Y_{\bar{D}}$, we obtain the ROC curve for covariates.

4.2 Direct Adjustment

This approach, contrasts with the approach set before. Instead of separately modeling the effect of covariate in the two distributions results of the diagnostic test and then obtains the ROC curve from the modified conditional distributions, direct adjustment model the covariate effects directly on the ROC curve. There are several advantages to the direct modeling approach. Foremost amongst them is that of any parameter associated with the covariate has a direct interpretation in terms of the curve. The heart of this approach is the specification of a suitable model that captures the effect of the covariate on the ROC curve, which allows a flexible and easy interpretation. The flexibility of the model is in terms of how this relationship works in the ROC curve, to preserve the condition that either the domain and the curve lie in the interval $(0,1)$ and that the curve continues to be monotone increasing in this range. The knowledge of least squares method to fit measures of variables, such as diagnostic test, and to evaluate the relationship between his results and the subject diseased status, suggested that the relationship between the ROC curve and the covariate effect was measured. This relationship is evaluated by using Generalized Linear Models (GLM). This methodology, leads the general form of the conditional ROC curve given by:

$$ROC_Y(p) = g\left(Y'\beta + h(p)\right), p \in (0,1) \tag{15}$$

where Y is a p-dimensional vector of covariates, β is a p-dimensional vector of unknown parameters, h is an unknown monotone increasing function of the $FPFs$, and g is a known link function, describing the functional relationship between the ROC curve and the covariates. Models such as (15) define the so-called class of ROC-GLMs [29].

The most common link functions are probit, logistic and logarithmic. Together with the advantage of directly evaluating the effect of the covariate on the ROC curve, direct methodology has some other appealing features:

– the ROC curve property of being invariant to monotonic transformation of
  the test result is preserved,
– any possible interaction between covariates and FPFs is easy to incorporate
  into the regression model,
– allows modeling the performance parameters and allows the comparison of
  different classifiers.

5   Application and Results

5.1   Study Description

In this work, to check if the age of the mother affects the discriminating ability
of the CRIB index, we used a sample of 187 infants of very low birth weight
(< 1500gr and/or gestational age < 32 weeks) from a hospital in North of
Portugal. Thus, the variable X will correspond to the CRIB, and the covariate
of interest will be the age of the mother. We will consider the age of the mother
as a binary variable, with reference to the age of 35 years old. So, we will have
two categories: age greater or equal than 35 years and younger than 35 years. Of
the 187 infants, 152 are newborns from mothers with less than 35 years old and
the remaining 35 are newborns of mothers aged 35 years or older. The rating
assigned according to the CRIB scale regarding their clinical status was, for the
first newborn mothers, 8.55% of the babies classified as "dead" and 14.29% of
the babies on the second group with the same classification. In the sample, 9.63%
of babies are classified as "dead".
To asses the objective of our study, we choose to apply the direct method, because
the advantages listed above.

5.2   Results

We begin by characterizing the distribution of babies, according to the classifi-
cation assigned by the CRIB scale, when we consider that the mother's age has
no effect on this classification and then considering this possible effect (Fig. 1).

According to this characterization, we obtained the respective empirical ROC
curves (Global and separately by mother's age) with R software, which are shown
in Fig. 2.

We compute the AUC, the standard deviation and the confidence intervals for
each of the ROC curves plotted above. These values are summarized in Table 1.

Obtained the intervals, with 95% of confidence, for the ROC curves, we pro-
ceed to its graphical representation to visualize possible dispersion of the pairs
of values $(1 - specificity, sensitivity)$. Figure 3 show the ROC curves with the
corresponding confidence interval, obtained by the application of R software.

To verify if maternal age has effect on the CRIB scale when used to classify
clinical babies status, we used the critical reason Z. The value computed by this
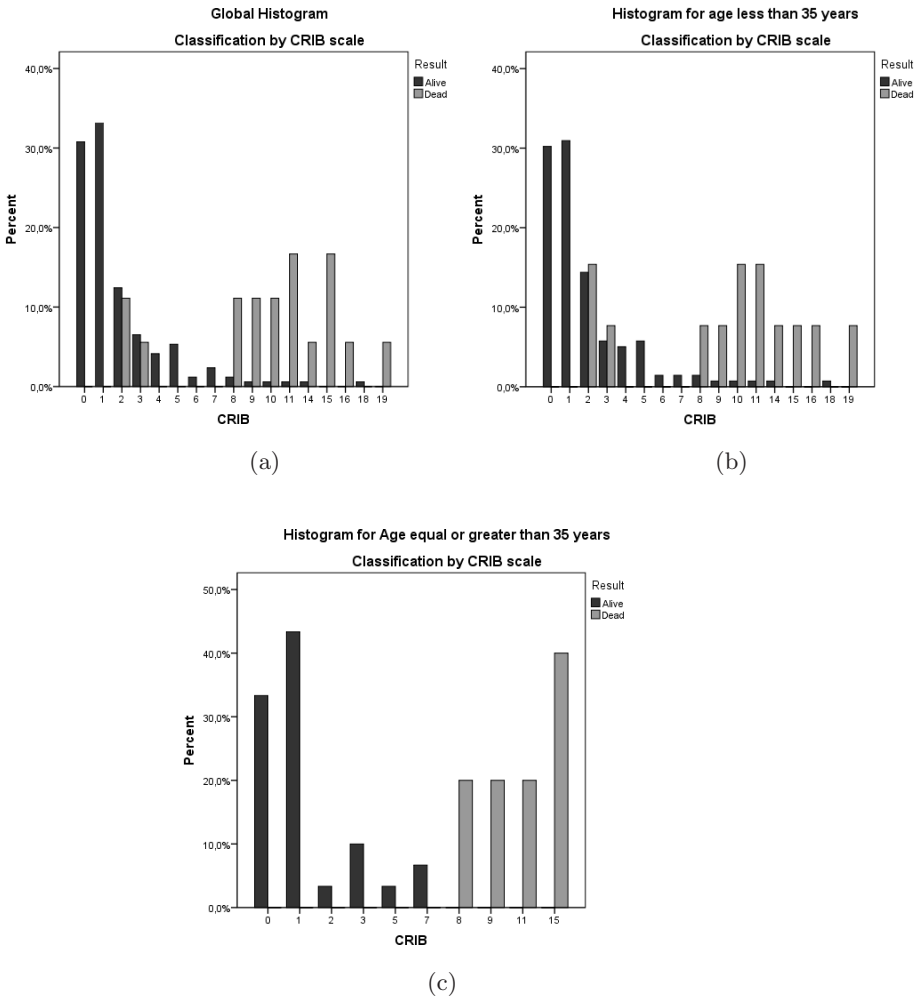statistic was $Z = 2.28$ ($p - value = 0.0226$).

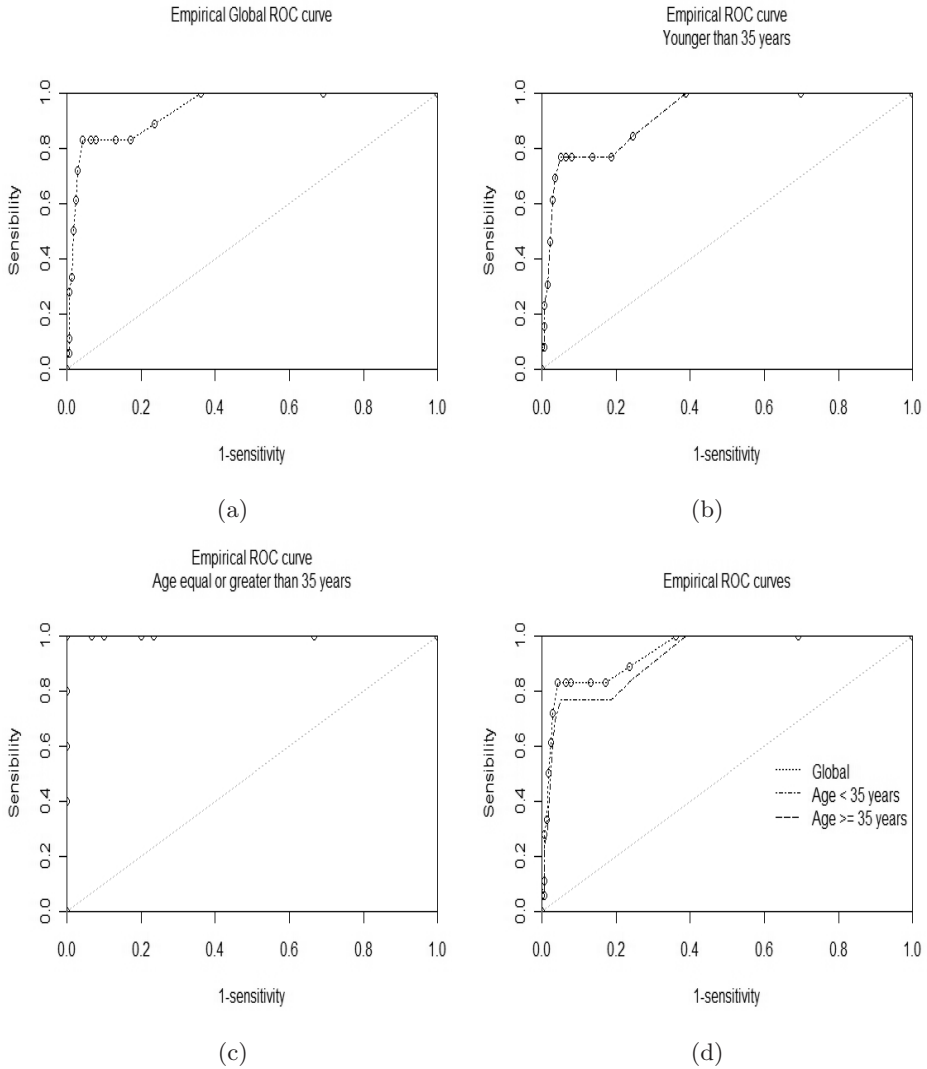**Fig. 1.** Histograms - classification assigned by the CRIB scale

Fig. 2. Empirical ROC curves (Global and separately by mother's age)

Table 1. ROC curves Results

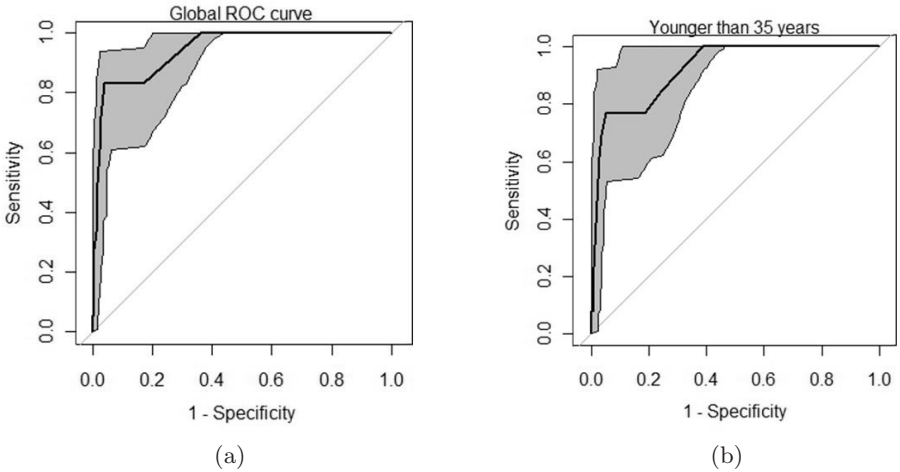|	AUC	SE	95% IC Lower Bound	95% IC Upper Bound
Global	0.942	0.025	0.8929	0.991
Maternal age less than 35 years	0.9203	0.035	0.8515	0.9891
Maternal age equal or greater than 35 years	1.000	6.8E-9	1.000	1.000

(a)   (b)

Fig. 3. ROC curves and Confidence Intervals

5.3   Direct Adjustment of Covariate with Stata Software

The results above suggest that the impact of maternal age on CRIB scale should be statistically adjusted in the ROC analysis. Stata software, using ROC regression, models the ROC curve (CRIB ROC curve) as a function of covariates (maternal age), via GLM. In statistic, the GLM is a flexible generalization of ordinary linear regression that allows for response variables that have error distribution models other than normal distribution. The GLM generalizes linear regression by allowing the linear model to be related to the response variable using a link function and by allowing the magnitude of the variance of each measurement to be function of its predicted value. We start by computing the graph of the ROC curve conditioned to maternal age (Fig. 4) with correspondent AUCs (Fig. 5) and test of equality of those areas (Fig. 6). The AUC for the conditioned CRIB ROC curve and the correspondent confidence intervals ((N)- normal confidence interval; (P) - percentile confidence interval; (BC) - bias-corrected confidence interval) is shown in (Fig. 7).
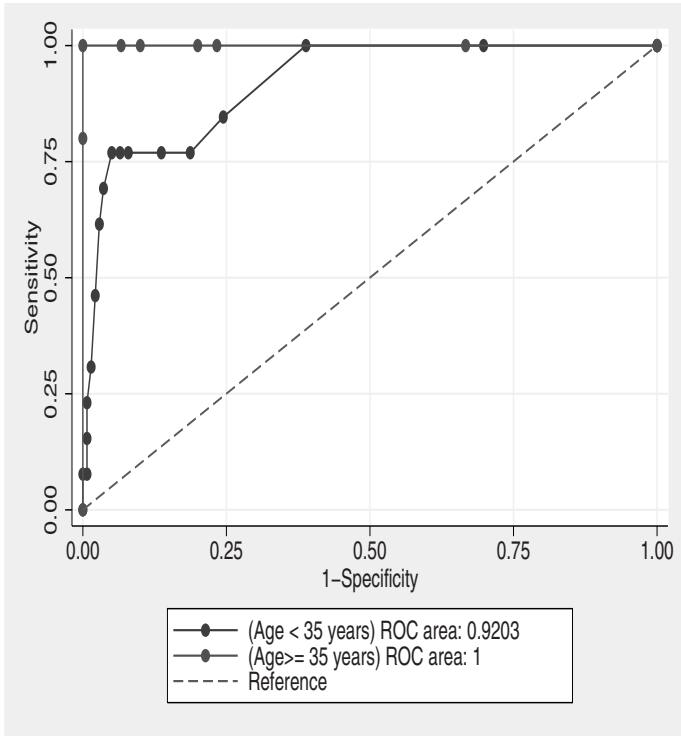
Fig. 4. ROC curve conditioned by Maternal Age (from STATA)

| | ROC | | —Asymptotic Normal — | |
Obs	Area	Std. Err.	[95% Conf. Interval]	
152	0.9203	0.0351	0.85153	0.98909
35	1.0000	0.0000	1.00000	1.00000

Fig. 5. AUCs for ROC curve conditioned by Maternal Age (from STATA)

Regarding the ROC curve for the CRIB, conditioned on maternal age, we found that the behavior is identical to that observed in the study described above with R software. The CRIB for age less than 35 year old mother discriminates 92.03% while for maternal age equal or greater than 35 years, discriminates in 100% of cases. We also found that a greater variability in the results is observed for the curve generated from the first data set. When performed the test of equality of the two areas, we found the following results:

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Ho: area(0) = area(1)
    chi2(1) =      5.16          Prob>chi2 =     0.0232
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Fig. 6. ROC curve conditioned by Maternal Age - comparison test (STATA output)

that leads to the rejection of the null hypothesis.

AUC	Observed Coef.	Bias	Bootstrap Std. Err.	[95% Conf. Interval]	
	.931255	.0009726	.0309972	.8705016	.9920084 (N)
				.8638773	.9858114 (P)
				.8551341	.9808154 (BC)

Fig. 7. AUC for the CRIB ROC curve conditioned by Maternal Age (STATA output)

By the results presented in (Fig. 7), we found a discrimination power for the CRIB ROC curve in 93.13% of the babies (AUC = 0.9313) and with a standard deviation equal to 0.0309. The confidence intervals to evaluate the dispersion of the pairs of values $(1 - specificity, sensitivity)$ was also computed.

6   Conclusions

From the estimated values of AUCs for the global ROC curve we may observe that, without considering the effect of maternal age, the CRIB scale discriminates between babies "alive" and "dead" in 94.2% of cases. This power, when considering maternal age as covariate, is 92.03% for age less than 35 years old and equal to 100% when maternal age is equal or greater than 35 years. We can see too, that the ROC curve for maternal age less than 35 year old shows greater variability (Table 1) and (Fig. 3). Applied the statistical test previously set out in Section 2 to determine whether maternal age has an effect on the classification of baby's, when CRIB scale is used, we conclude that there is a significant difference in the performance of CRIB scale when conditioned on maternal age and maternal age equal or greater than 35 years old has effect on the discrimination power of CRIB scale. From the results obtained above, it is apparent that mother's age appears to affect the discriminatory power of CRIB scale when used to classify babies. For this reason, we consider useful to verify the performance of this scale when conditioned on maternal age by using the ROC-GLM regression models (CRIB ROC analysis with correspondent CRIB ROC curve). The results presented in (Fig. 7) suggest that the performance of CRIB scale decreases when one incorporates the age of the mother in her review (AUC = 0.9313). The standard deviation, in turn, is greater than the standard deviation of the ROC curves obtained without the covariate. Consequently, it also increases the dispersion of the pairs of values $(1 - specificity, sensitivity)$.

Fig. 6 shown the results for comparison test by the STATA software that indicated also that maternal age has effect on the classification of babies by the CRIB scale. CRIB scale perform better for maternal age equal or greater than 35 years old.

Motivated by these results we propose as future work, to check if the sex of the babies along with the mother's age, also have an effect on the classification of infants when using the CRIB scale.

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