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Original Article

A New Score for Predicting Neonatal Very Low Birth Weight Mortality Risk in the NEOCOSUR South American Network

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OBJECTIVE:

To develop and validate a model for very low birth weight (VLBW) neonatal mortality prediction, based on commonly available data at birth, in 16 neonatal intensive care units (NICUs) from five South American countries.

STUDY DESIGN:

Prospectively collected biodemographic data from the Neonatal del Cono Sur (NEOCOSUR) Network between October 2000 and May 2003 in infants with birth weight 500 to 1500 g were employed. A testing sample and crossvalidation techniques were used to validate a statistical model for risk of in-hospital mortality. The new risk score was compared with two existing scores by using area under the receiver operating characteristic curve (AUC).

RESULTS:

The new NEOCOSUR score was highly predictive for in-hospital mortality (AUC = 0.85) and performed better than the Clinical Risk Index for Babies (CRIB) and the NICHD risk models when used in the NEOCOSUR Network. The new score is also well calibrated — it had good predictive capability for in-hospital mortality at all levels of risk (HL test = 11.9, $p = 0.85$). The new score also performed well when used to predict in hospital neurological and respiratory complications.

CONCLUSIONS:

A new and relatively simple VLBW mortality risk score had a good prediction performance in a South American network population. This is an important tool for comparison purposes among NICUs. This score may prove to be a better model for application in developing countries.
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INTRODUCTION

Risk-adjusted mortality has been used to compare hospital's performance. To accomplish this task, risk models have been developed to adjust raw mortality rates for patient risk differences.[1–4]

Development of a mortality risk measure is essential to compare outcomes across neonatal intensive care units (NICUs). Evaluation of medical practices, benchmarking purposes and quality of care comparisons require accurate and reliable risk models. Several neonatal mortality risk scores have been developed, including the Clinical Risk Index for Babies (CRIB) by the International Neonatal Network,[1] the NICHD score developed by Horbar et al.,[2] and the Score for Neonatal Acute Physiology and Score for Neonatal Acute Physiology II (SNAP and SNAPPE-II) by Richardson et al.[5,6] All of these scores have been developed using outcomes from NICU networks in developed countries, where the

human and technical resources are very similar with few limitations.

The purpose of this study was to develop a neonatal mortality risk score for very low- birth- weight (VLBW) infants based on variables present at birth, before neonatal intensive care unit (NICU) admission in a multicenter South American Network with diverse mortality rates and resources.

METHODS

All infants with birth weight 500 to 1500 g born from October 1, 2000 to May 30, 2003 in 16 Neonatal del Cono Sur (NEOCOSUR) Network participating centers from Argentina, Chile, Paraguay, Peru and Uruguay were included in this study. Biodemographic information and outcome data are prospectively and routinely collected in the NEOCOSUR Network using predefined diagnostic criteria and online data entry. Delivery room deaths were included.

The following risk factors associated with adverse outcome were included in the model: maternal age, birth weight, gestational age, 1 minute Apgar score, major acute life-threatening (ALT) congenital malformations, sex of the infant, multiple birth, prenatal steroids use, and small for gestation age (defined as lower than the 10th percentile of weight for their gestation age according to a Chilean national growth curve[7]) were studied. ALT congenital malformations included diaphragmatic hernia, major congenital heart disease, intestinal atresia, hydrops, and inborn errors of metabolism, as in the CRIB study. The candidate risk factors were chosen among the ones described in other studies and based on variables present at birth. Univariate association between these infant risk factors and mortality were performed using a simple logistic regression model for categorical variables and a generalized logistic additive model for continuous variables. This model was used to assess the form of the effect of the continuous variables, using nonparametric curve estimation.

A stepwise multiple logistic regression model was used to select the subset of variables that were independently associated with mortality. A significance level of 5% was used to include a variable in the model. With the development of the final model, we were able to estimate the probability of in-hospital mortality for each infant based on prenatal and admission risk factors.

The model was developed using a random sample consisting of 75% of the cases (model sample, $n = 1351$). The rest of the data were set aside for model validation purposes (test sample, $n = 450$). A secondary strategy of validation was used using crossvalidation techniques.[8] We used our final multiple logistic regression model for crossvalidation, by using it to obtain predicted mortality estimates for each infant ($n = 1801$), based on data from all other infant. This provided an alterative assessment of the predictive capability and calibration of our model.

To assess the predictive capability of the model, the area under the curve[9] (AUC) was calculated using the model sample, the test sample and the total sample using crossvalidation techniques. Comparisons with other risk scoring were carried out using Bootstrap confidence intervals of differences in AUC.[10] The calibration of the model was performed using the Hosmer–Lemeshow test.[11] The statistical analysis was done using Splus software.[12]

The model was also used to predict in-hospital relevant respiratory and neurological complications. Bronchopulmonary dysplasia (BPD) was defined as an oxygen requirement at 28 days of life and chronic radiographic changes.[13] Oxygen dependency at 36 weeks postmenstrual age was considered a separate diagnosis. The diagnosis of intraventricular hemorrhage (IVH) was made by cranial ultrasonography (this was carried out at least twice, in the first week of life, and at 3 to 4 weeks age) or by autopsy and was classified according to Papile et al.[14] Periventricular leukomalacia (PVL) was diagnosed by the presence of focal echolucencies on the cranial ultrasound.

RESULTS

The study population included 1801 infants. The mean birth weight was 1081 g, and the mean gestational age was 29.2 weeks. Male infants represent the 49.4% of the total population. The mean mortality rate among the different centers was 26.7% with a range of 9.7 to 51.8% among units.

Table 1 shows descriptive statistics comparing survivors and nonsurvivors. In average, survivors have more birth weight, gestational age, and 1-minute Apgar than nonsurvivors. Additionally, survivors have less congenital malformations and male infants than nonsurvivors.

Table 2 displays the univariate associations between in-hospital mortality and prenatal and admission infant characteristics. Birth weight was the best predictor of mortality (AUC = 0.79), followed by gestational age (AUC = 0.77) and 1-minute Apgar score with the same association level (AUC = 0.77). Other factors that were significantly associated with in-hospital mortality were ALT congenital malformations, prenatal steroid use, maternal age, and small for gestational age.

The effects of each of the quantitative variables on in-hospital mortality were analyzed using generalized additive logistic regression models. All variables except maternal age showed linear effect; therefore, the data were entered into the multiple logistic regression model as they were originally measured, without breaking them into range categories.

When a multiple logistic regression model with a step-wise procedure was used, six factors were statistically significant in order of significance: birth weight, gestational age, 1-minute Apgar score, ALT congenital malformation, antenatal steroid administration, and female gender of the infant. Table 3 shows the coefficients of the multiple logistic regression model, the standard error and the

Table 1 Comparison of Population Characteristics between VLBW Infants Survivors and Nonsurvivors in Relation to Factors used to Construct the NEOCOSUR Risk Score

Factor	Survivors ($n = 1322$)	Nonsurvivors ($n = 479$)
Birth weight (grams)	1161±6.7	863±11.9
Gestational age (weeks)	30.1±0.1	27.0±0.1
1-minute Apgar	6.6±0.1	3.9±0.1
ALT congenital malformation	0.3%	7.7%
Prenatal steroids use	74%	53%
Mother's age (years)	28±0.2	26±0.3
Small for gestation age*	45%	53%
Female gender	52%	46%
Multiple Birth	19%	15%

ALT = acute life threatening.
*Defined as lower than the 10th percentile of weight for their gestation age.[7]
Mean±SEM or percentage when appropriate.

Table 2 Univariate Association between In-Hospital Mortality and Preadmission Infant Characteristics

Factor	χ^2 test	p-value
Birth weight per 100 g	343.6	<0.01
Gestational age per week	290.3	<0.01
1-minute Apgar	289.9	<0.01
Congenital malformation	63.3	<0.01
Prenatal steroids use	52.1	<0.01
Mother's age	7.8	<0.01
Small for gestation age*	4.1	0.04
Female gender	3.2	0.07
Multiple Birth	2.1	0.15

*Defined as lower than the 10th percentile of weight for their gestation age.[7]

associated odds ratios. These coefficients for the six selected variables in the context of a logistic model constitute the NEOCOSUR score and can be used to calculate predictive risk of VLBW infant mortality. An increase of 100 g in birth weight reduced the risk of in-hospital mortality by 28%. Similarly, one addition point in the 1-minute Apgar score reduced the risk by 23%. One additional week of gestation age reduced the risk by 12%. ALT congenital malformation had the largest effect size among all the risk factors — it increases the risk of neonatal mortality by more than five times. However, the population attributable risk due to this factor would be relatively small because ALT congenital malformations have an incidence of only 2.2%.

Table 4 shows the predictive capability of the NEOCOSUR score as compared to the CRIB and the NICHD scores using the area under the receiver operator curve (ROC) (AUC). The NEOCOSUR risk score had a high predictive ability (AUC = 0.88) when it was evaluated on the model sample ($n = 1351$); however, its predictive ability was reduced to 0.84 when it was used to predict mortality in the test sample ($n = 450$). When the NEOCOSUR score was evaluated in the two combined samples, the AUC was 0.87. As an alternative to the testing sample, the NEOCOSUR score had an AUC of 0.85 when crossvalidation techniques were used. The NEOCOSUR had better predictive capacity for in-hospital neonatal mortality than either the CRIB and NICHD scores, or birth weight alone.

Table 3 Factors Selected by a Stepwise Logistic Regression Model that Constitute the NEOCOSUR Score for Predicting VLBW Infant Mortality

Factor	Coefficient	SE	Odds ratio	95% CI
Constant	8.378	0.99	—	—
Birth weight	−0.331	0.04	0.72	0.64–0.79
Gestational age	−0.132	0.04	0.88	0.80–0.95
1-minute Apgar	−0.265	0.03	0.77	0.71–0.82
Congenital malformation	3.419	0.64	30.55	8.74–106.77
Prenatal steroids use	−0.302	0.08	0.74	0.58–0.89
Female gender	−0.474	0.16	0.62	0.30–0.93

Table 4 Predictive Capability of Various Neonatal Mortality Risk Scores using the Area Under the ROC Curve (AUC), Including the NEOCOSUR Score

Risk score	Sample	AUC
NEOCOSUR	Model	0.88
	Test	0.84
	Total	0.87
	Crossvalidation	0.85
CRIB	Total	0.79
NICHD	Total	0.83
Birth weight	Total	0.79

The 95% confidence interval for the difference between the AUC of the NEOCOSUR score, using crossvalidation result, and the CRIB score was 0.037 to 0.081 and between the AUC of the NEOCOSUR score and the NICHD score was 0.019 to 0.040. With these results, we can conclude that the NEOCOSUR score is significantly better predictor of mortality for this population.

Figure 1 shows the ROC curve resulting from the NEOCOSUR score using the crossvalidated score estimate, the NICHD score, and the CRIB score in all observations ($n = 1801$). The NEOCOSUR score had higher sensitivity than the NICHD and CRIB scores, for all levels of specificity.

Figure 2 shows the goodness of fit of the NEOCOSUR score by comparing the observed versus estimated mortality rate for each deciles group of risk score. A Hosmer–Lemeshow goodness of fit test ($\chi^2 = 11.9$, degree of freedom = 8, $p = 0.85$) confirms that the NEOCOSUR score assess mortality rate well at all levels of risk.

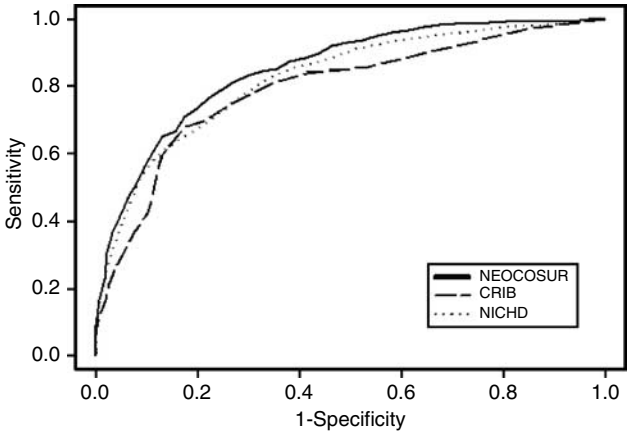

Figure 1. ROC curves for in-hospital mortality for NEOCOSUR, CRIB, and NICHD risk scores.

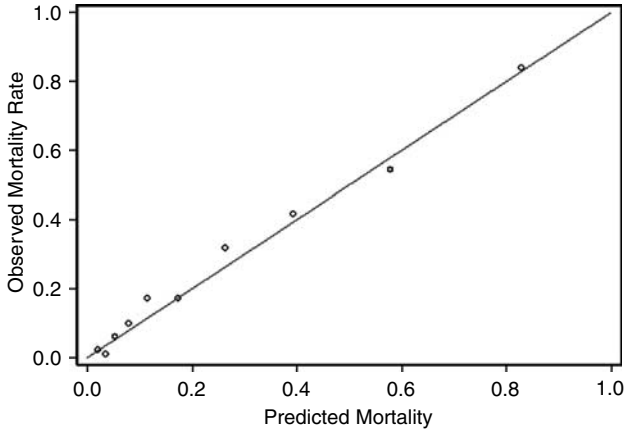

Figure 2. Observed mortality rate by decile of predicted mortality for VLBW infants ($n = 1801$). The predicted mortality was calculated based on a logistic regression model. The dots represent the observed mortality rate of the decile groups and the continuous line represent perfect model calibration.

When the NEOCOSUR score was used to predict in-hospital neurological and respiratory complications among VLBW infants that survive to hospital discharge (Table 5), there was good predictive ability for BPD at 28 days (AUC = 0.81) and oxygen requirement at 36 weeks postmenstrual age (AUC = 0.77), but slightly lower values for IVH grades III to IV grade (AUC = 0.72) and PVL (AUC = 0.69). When compared with the CRIB and NICHD risk scores, NEOCOSUR score shows similar predictive capability for these morbidities.

Table 5 Area under the ROC for Adverse Outcomes Among Surviving Infants using the NEOCOSUR, CRIB and NICHD Scores

In-hospital complications	AUC of risk score		
	NEOCOSUR	CRIB	NICHD
Severe ICH	0.72	0.77	0.69
PVL	0.69	0.75	0.67
Oxygen 36 weeks	0.77	0.72	0.76
BPD	0.81	0.76	0.80
HIC Grade III–IV	0.72	0.77	0.69

Severe ICH = grade III to IV IVH (cite Papile); PVL = periventricular leukomalacia.

DISCUSSION

There is a wide variation in VLBW infant mortality rates in South America, as reported previously.[15] The reported sample was born in NEOCOSUR Network centers that are university affiliated and belong to the public and private health-care systems, but vary in size, population served, and resources, the in-hospital mortality rates ranged from 9.7 to 51.8%. We developed a new relatively simple mortality prediction model for VLBW infants that could be successfully applied soon after birth in an area such as South American that has diverse levels of care and population risks.

We tested for commonly available factors that are present before the 1-minute Apgar score, so that prediction would not be influenced by postnatal interventions. We studied several variables that affect mortality, and selected the ones that were most highly associated with mortality. Birth weight was found to be the variable most predictive of in-hospital mortality, followed by gestational age, and 1-minute Apgar score. Although birth weight is recognized as a major determinant of neonatal mortality, it is inadequate to explain the large variations in neonatal mortality among NICUs,[16] so a mortality risk score is required.

The model was validated using two alternative methods. First, the model was validated using a test sample not used for model development, and second, the model was validated using crossvalidation techniques, a leave-one-out resampling method. Both methods consistently showed that the NEOCOSUR score has better predictive capabilities than the CRIB and NICHD scores for in-hospital mortality in this population.

Our model performed better than the CRIB and NICHD models. CRIB was developed in the United Kingdom ($n = 1300$; birth weight <1500 g) and published in 1993. It consists of six items, including birth weight, gestational age, congenital anomalies, and three physiological measures obtained during the first 12 hours of age. SNAP was developed in the Unites States ($n = 1643$ admissions) and published in 1993, and includes newborns of all birth weight. It consists of 34 items collected in the first 24 hours of admission. We were unable to compare our results with the Score for Neonatal Acute Physiology (SNAP) because we did not have all the information about the items required. The NICHD score was developed in the United States ($n = 3603$ infants 501 to 1500 g)

and was also published in 1993. It consists of five items including birth weight, small for gestational age, black race, male gender, and 1-minute Apgar score. These scores have been replicated with good to excellent performance in most reports,[17] although with occasional poor performance and no better than birth weight alone.[18,19] In recent years, Pollack et al.[20] has published risk models in a cohort of VLBW infants from the Washington, DC area. They found that these scores overpredicted mortality indicating a need for frequent recalibration. A need for periodic revalidation of risk models has been addressed in the past.[17] There have also been other efforts in individual centers to create their own risk score.[21]

Our model differs from the CRIB and SNAP risk scores in that it has fewer variables and the information is collected upon admission; therefore, it is less dependent on postnatal interventions. In this regard, our model is similar to that of the NICHD. The main difference between the NICHD score and the NEOCOSUR score is that the NICHD score includes race that does not apply in the South American population and our model uses the Apgar score as a continuous variable. Our score is similar to other risk scores in providing an objective initial mortality risk prognosis, but it does not predict the risk for an individual infant and therefore cannot be used to justify the withdrawal of therapy or to limit care.

This new model is primarily designed to be use for mortality risk prediction, although we also found that it may predict serious in-hospital respiratory and neurological complications. However, this last finding is expected since BPD and IVH are closely related to infant's birth weight and gestational age. Its usefulness in predicting long-term outcome has not been tested. Tests of the CRIB score suggest that it is not a reliable tool for predicting neurodevelopmental outcome.[22]

An obvious limitation of the NECOSUR risk score is that only applies to VLBW infants, under 1500 g of birth weight.

We conclude that this new and relatively simple neonatal VLBW infant mortality risk score has good predictive performance in a multicenter South American population, and is an important tool for comparison purposes among NICUs. Based on its simplicity and good performance in a diverse population setting, we speculate that this risk score may prove to be a better model for application in developing countries.

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Appendix A1

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