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Development and validation of the Neonatal Mortality Score-9 Mexico to predict mortality in critically ill neonates

Horacio Márquez-González, M. Sc.[a], María Valeria Jiménez-Báez, MD[b], C. Mireya Muñoz-Ramírez, M. Sc.[c] Lucelli Yáñez-Gutiérrez, M. Sc.[a], Ana C. Huelgas-Plaza, MD[d], Eduardo Almeida-Gutiérrez, MD[e], and Antonio Rafael Villa-Romero, MD[f]

a. Hospital de Cardiología, Centro Médico Nacional Siglo XXI, Instituto Mexicano del Seguro Social.
b. Research Coordination, Cancún, Quintana Roo.
c. Instituto Nacional de Pediatría.
d. Hospital de Ginecología y Obstetricia #4 " Dr. Luis Castelazo Ayala".
e. Health Research Coordination, Instituto Mexicano del Seguro Social.
f. Department of Research of the Facultad de Medicina of the Universidad Nacional Autónoma de México.

E-mail Address:
M. Sc. Horacio Márquez-González: horacioinvestigacion@hotmail.com

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ABSTRACT

Introduction. Prognostic scales or scores are useful for physicians who work in neonatal intensive care units. There are several validated neonatal scores but they are mostly applicable to low birth weight infants. The aim of this study was to develop and validate a mortality prognostic score in newborn infants, that would include new prognostic outcome measures.

Population and Methods. The study was conducted in a mother and child hospital in the city of Mexico, part of the *Instituto Mexicano del Seguro Social* (Mexican Institute of Social Security). In the first phase of the study, a nested case-control study was designed (newborn infants admitted on the basis of severity criteria during the first day of life), in which a scale was identified and developed with gradual parameters of cumulative score consisting of nine independent outcome measures to predict death, as follows: weight, metabolic acidemia, lactate, PaO_2/FiO_2, p(A-a) O_2, A/a, platelets and serum glucose.Validation was performed in a matched prospective cohort, using 7-day mortality as an endpoint.

Results. The initial cohort consisted of 424 newborn infants. Twenty-two cases and 132 controls were selected; and 9 outcome measures were identified, making up the scale named neonatal mortality score-9 Mexico. The validation cohort consisted of 227 newborn infants. Forty-four (19%) deaths were recorded, with an area under the curve (AUC) of 0.92. With a score between 16 and 18, an 85 (11-102) hazard ratio, 99% specificity, 71% positive predictive value and 90% negative predictive value were reported.

Conclusions. The proposed scale is a reliable tool to predict severity in newborn infants.

Key words: *child mortality, neonatal intensive care units, risk factors, disease severity index.*

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INTRODUCTION

Reducing mortality in children under five is one of the Millennium Development Goals.[1]

Worldwide averages show that four million children die during the first four weeks of life. The main causes are prematurity, asphyxia and sepsis.[2] Intervention through preventive measures has managed to reduce up to 67% of neonatal mortality.[3]

In Mexico,[4] 2 271 700 deaths were registered in 2003; 20 806 of those deaths occurred during the neonatal period; 49.4% of them were associated to asphyxia.

Detection of critically ill newborn infants offers the possibility of a timely treatment that would have a direct impact on survival and decrease morbidity. Prognostic scales are useful for physicians working in neonatal intensive care units (NICUs). There are scales or scores used at an international level:[5] SNAPPE[6] (*Score for Neonatal Acute Physiology Perinatal Extension*), CRIB II[7] (*Clinical Risk Index for Babies Score*) and NEOCOSUR (Neonatal del Cono Sur).[8] They are mostly used in premature infants weighing under 1500 g.

This study proposes the development and validation of a score to predict mortality in critically ill newborn infants, without excluding those weighing above 1500 g, based on the inclusion of new prognostic factors.

POPULATION AND METHODS

With the authorization of the local institutional review board (R-2012-6790-89), the study was conducted in Hospital General of Zona 2 A Troncoso, from the *Instituto Mexicano del Seguro Social* (IMSS), and comprised the following phases:

a) Identification of possible predictive outcome measures: From January 2005 to December 2010, a cohort was prospectively defined inclu-

ding newborn infants of any gestational age, both genders, multiple gestations and visible external malformations. They had to be delivered at the Obstetrical-Surgery Unit of the Hospital, admitted at the NICU on their first day of life and under care until discharged for any cause. Patients born in other units were excluded and newborn infants voluntarily withdrawn by their parents or transferred to other hospitals were removed. The sample size calculation was based on the previous year statistics, with a total of 3450 births and 11% mortality, a= 95% and d= 99% (0.001), replaced in the odds ratio formula for finite population,[9] with an estimate patient number of 204. A 10% was added to make up for estimated losses, resulting in a final calculation of 224 patients.

b) Association with the outcome measure: Several prenatal outcome measures were investigated: threatened preterm labor, prenatal infections, diabetes, preeclampsia, premature rupture of membranes and prenatal administration of steroids. Perinatal outcome measures were: Apgar and Silverman-Andersen score at one and five minutes, gestational age by Capurro in newborn infants older than 32 weeks of gestational age and Ballard score in those under 28 weeks of gestational age, weight for gestational age, as well as outcome measures upon admission at the NICU as follows: blood gases, blood count and blood chemistry determined during the first hour, ventilation parameters: p(A-a) O_2, paO_2/FiO_2, A/a. The time of admission at the NICU was considered as baseline.The endpoint was 7-day mortality rate.

   Patients who died up to day 7 were considered "cases", and all patients remaining alive up to this timepoint were considered "controls". Six controls were randomly selected per each case (using the Aleator Method software for Excel).

c) Assessment of prediction capacity using an independent model: A univariate association of risk variables was conducted, and those found to be significant were subjected to a logistic regression analysis. Nine independent outcome measures were identified (weight, Apgar at five minutes, metabolic acidemia, lactate, alveolar-arterial gradient and ratio, Kirby index and glucose).

d) Development of the scale scoring system: Outcome measures resulting from the final model were scored based on the significance of the statistical association reported by other authors (prognosis and meta-analysis articles).[10-18] Results obtained were compared to those from the first cohort: values reported as normal and within the median were considered as 0 points; values corresponding to the 3rd quartile, 1 point; and the value from the last quartile, 2 points (*Table 1*). The scale was named Neonatal Mortality Score-9 Mexico (EMN-9 Mex).

e) Calculation of the diagnostic accuracy of the scale: individual scores were added up and a ROC curve was developed to determine the best cut-off point and to calculate the area under the curve. Stratification was chosen using the items corresponding to values of 1-sensitivity of the following ranges: < 0.5; 0.51-0.75; 0.76-0.94 and ≥ 0.95.

f) Prospective validation of the scale: A prospective cohort of newborn infants was designed using data from January 2010 to December 2012. Selection criteria were the same as for the previous cohort. Follow up started at the time newborn infants were admitted at the NICU. Outcome measures included in this scale were taken within the first hour of admission Based on the first phase of the study that included 424 patients admitted in the NICU, with a 5% mortality rate (a= 95% and d= 99%), the odds ratio for a finite population was estimated resulting in a required sample size of 90 newborn infants. A 10% was added for losses and 10 patients were added per outcome measure (90), resulting in a final size of 189 patients.

Statistical analysis: for the descriptive statistics central trends (s median) and scatter (interquartile ranges) were used for quantitative outcome measures, and frequencies and percentages were used for qualitative outcome measures. In the first cohort, the risk by odds ratio (OR) was calculated and a logistic regression analysis was performed. For the second cohort, a Cox analysis was carried out and the hazard ratio (HR) was calculated; survival analysis by Kaplan Meier and validity tests (sensitivity, specificity, predictive values, likelihood values and area under the curve) were performed for each of the strata proposed.

The Statistical Package for the Social Sciences (SPSS), version 20 for Windows was used in the statistical package.

RESULTS

First cohort: 424 newborn infants met the eligibility criteria. Twenty-two cases were presented and 132 controls were randomly selected (*Figure 1.A*). Differences between cases and controls, as well as risk calculation and adjustment are shown in *Table 2*.

Second cohort: During the study period, there was a total of 7 300 deliveries, out of which 306 newborn infants were admitted at the NICU. Finally, 227 patients were included (*Figure 1.B*). On average, the early neonatal mortality rate was 8.5 newborn infants per 1000 births; 133 (58%) were classified as very low birth weight for gestational age.

Of the participants, 140 (61%) were male; the median gestational age was 33 weeks (24-39); the median weight was 1100 g (780-2100); and the median height was 43 cm (38-48). Forty-four deaths (19%) were registered.

The score area under the curve was 0.92, p <0.0001, for mortality prediction; the confounder-adjusted HR of each stratum is shown in *Table 3*. The validity of each stratum is shown in *Table 4.* Cumulative survival probability by day 7 was 81%. *Figure 2* shows survival by scoring strata.

DISCUSSION

Scales are tools used in medical practice to predict the behavior of a disease, they signal the development of complications or death and are useful for the subsequent evaluation of healthcare programs.[19]

The population of the hospital where the study was conducted matches the population characteristics of most cities. Causes of death agree with epidemiology reports from Mexico and the rest of the world.[4]

In the first cohort, factors associated with death were identified, and results showed that independent outcome measures in the multi-cause model were consistent with those found by other authors; some of these were items of already validated scores.[6] However, other outcome measures, such as ventilation and diffusion rates, platelets and hyperglycemia are new compared to the previously mentioned scales.

Perinatal outcome measures did not prove to be useful in our prognostic model; this phenomenon had already been contemplated by the SNAP (Score for Neonatal Acute Physiology) scale in 2001,[20] but ours differs from the NEOCOSUR scale,[8] that does include prenatal variables.

It is worth mentioning that prenatal steroid administration did not prove to be significant on the final model, which differs from reports of the NEOCOSUR group,[8] probably because the population is not held at the study center and the time necessary to artificially induce lung maturation is not enough.

Prematurity is the main comorbidity associated with death and it is represented in our scale by birth weight (due to the likelihood of multi-co-linearity, it was managed this way in our score), given the known relationship between low birth weight and mortality.[21,22] We consider this finding is timely taking into account that estimating gestational age may not be so

TABLE 1. *Scale to predict mortality in critically ill newborn infants (EMN - 9 Mex)*

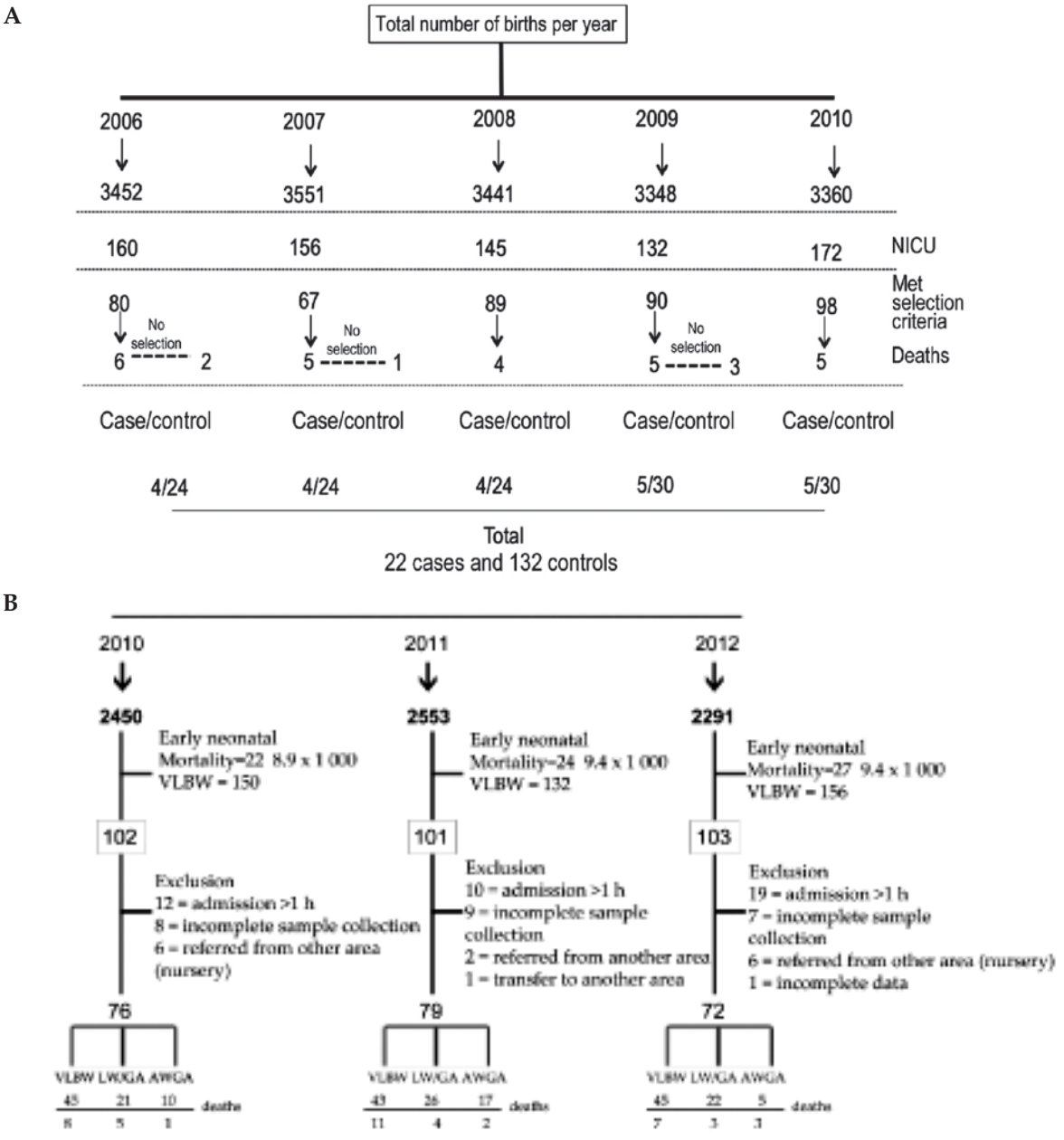
Outcome measure	Score		
	0	1	2
Apgar score at five minutes (points)	From 9 to 10	From 7 to 8	≤ 6
Birthweight (g)	≥ 2500	From 1500 to 2499	≤ 1499
Blood gases*	Normal	Metabolic acidosis	Metabolic acidosis of AG** ≥ 15
Lactate (mmol/L)	≤ 1	1.1-3.9	≥ 4
PaO_2/FiO_2 (mm/Hg)	≥ 350	From 200 to 349	≤ 199
P(A-a) O_2 (mm/Hg)	≥ 100	101-299	≥ 300
A/a	≥ 0.6	0.5-0.26	≤ 0.25
Platelets (cell/μL)	≥ 150 000	50 000-149 000	≤ 50 000
Serum glucose (mg/dL)	≤ 126 mg/dL	From 127 to 200 mg/dL	≥ 201 mg/dL

* Acidosis: pH ≤ 7.28 and base excess below 6 mmol/L.
** Anion gap (AG): Na - (HCO_3 + Cl).

reliable to indicate prematurity considering all the chances of variability in the interpretation of rating tools, even among pediatricians.[23]

Perinatal asphyxia is one the main causes of death and it is biologically plausible that a low Apgar score and metabolic acidemia are part of the scale.[24] Respiratory disorders, such as respiratory distress syndrome, intrauterine pneumonia or meconium aspiration syndrome are the main comorbidities and their severity affects oxygen diffusion in different degrees. PaO_2/FiO_2 ratio infers lung damage, whilst p(A-a) O_2 considers the difference between alveolar and capillary oxygen, and A/a shows the same

FIGURE 1. *Selection scheme of the first cohort (A) and the second cohort (B) subjects*



CS: met selection criteria. VLBW: very low birth weight. AWGA: appropriate weight for gestational age. LW/GA: low weight for gestational age. NICU: Neonatal Intensive Care Units.

phenomenon without estimating the FiO_2 effect.[26] The result from both formulas points at a disorder at the alveolar-capillary membrane level.

Hypoperfusion states alter lactate and glucose levels[27] and platelet function.[28] Taking into account that most neonatal comorbidities impair tissue oxygen diffusion, it is reasonable that they remain as independent variables and form part of the scale.

None of the previously published scales or scores include hyperglycemia as a mortality-related factor. Glucose levels are increased because there is an immaturity in insulin secretion and are associated with conditions that cause death, such as intraventricular hemorrhage, sepsis, necrotizing enterocolitis, among others.[30]

The validation cohort of EMN-9 Mex was consistent with the group of patients of the original cohort, in which items constituting this scale arose. All the outcome measures included in the scale kept their significance.

Most mortality scales use βcoefficients to determine the predictive weight of their variables. It is difficult to substitute such values in daily practice; for this reason we considered that the development and interpretation of the EMN-9 Mex had to be easy, based on simply adding up points to obtain a score because users are

TABLE 2. *First phase results: comparison of risk factors between live and dead newborn infants*

Outcome measure	Live n= 132	Dead n= 22	OR (CI 95%) raw	OR (CI 95%) adjusted
Preeclampsia	21 (16%)	3 (13%)	0.7 (0.1-3.7)	0.8 (0.3-19)
Gestational diabetes	22 (17%)	6 (25%)	1.4 (0.5-6)	2 (0.3-23)
External malformations	16 (12%)	4 (20%)	1.7 (0.9-7)	2.4 (0.7-15)
Threatened preterm labor	9 (7%)	1 (5%)	0.8 (0.09-6.9)	0.4 (0.2-5)
Multiple pregnancy	8 (6%)	1 (5%)	0.8 (0.7-1.3)	0.4 (0.3-8)
Third trimester infections	21 (16%)	3 (13%)	0.7 (0.1-3)	0.8 (0.5-13)
Premature rupture of membranes > 8 h	25 (19%)	7 (32%)	1.7 (0.5-5.8)	1.3 (0.4-14)
Prenatal steroids	22 (17%)	1 (5%)	**0.8 (0.7-0.9)**	0.6 (0.1-1.1)
Apgar < 6 at one minute	46 (35%)	15 (70%)	**4 (1.3-12)**	1.4 (0.8-14)
Apgar < 6 at five minutes	12 (9%)	8 (38%)	**5.9 (1.8-19)**	3.5 (1.7-5)
SA > 3 at one minute	30 (23%)	11 (50%)	**3.1 (1.1-9.2)**	14 (0.4-20)
SA > 3 at five minutes	67 (51%)	15 (69%)	2 (0.6-6.2)	3 (0.2-7)
Gestational age				
> 37 weeks	93 (70%)	4 (18%)	**0.03 (0.01-0.7)**	-
32-36.6 weeks	30 (23%)	11 (50%)	**2.3 (1.2-7)**	1.2 (0.4-1.9)
< 31.6 weeks	9 (7%)	7 (32%)	**3.1 (1.7-8.9)**	1.5 (0.9-12)
Weight (g)				
> 2500	86 (65%)	5 (22%)	**0.4 (0.1-0.7)**	-
1500-2499	33 (25%)	7 (33%)	**2.4 (1.3-6.5)**	-
< 1499	13 (10%)	10 (45%)	**5 (2.3-8)**	**4.3 (2-5.4)**
Gender				
Male	53 (40%)	8 (37%)	1.01 (0.9-1.1)	-
Female	79 (60%)	14 (63%)	0.9 (0.3-2.2)	0.5 (0.3-13)
Metabolic acidemia	72 (55%)	20 (91%)	**1.5 (1.2-9)**	**1.7 (1.2-3.2)**
Elevated anion gap (> 15)	46 (35%)	31 (70%)	**6 (2-10)**	**2.8 (1.5-5.8)**
Lactate > 4 mmol/L	33 (25%)	20 (91%)	**23 (6-310)**	**12 (3-17)**
Hemoglobin< 9 g/dL	5 (4%)	2 (10%)	1.3 (0.6-5)	1.1 (0.5-1.5)
Platelets< 100 000 cell/µL	9 (7%)	7 (32%)	**5.4 (1.5-18)**	**2.9 (2-4.3)**
A/a< 0.23	66 (50%)	20 (91%)	**1.7 (1.1-1.5)**	**1.3 (1.1-2)**
$P(A-a)O_2$	59 (45%)	21 (95%)	**1.8 (1.2-2)**	**1.4 (1.2-3)**
paO_2/FiO_2 < 200	106 (80%)	21 (95%)	**1.8 (1.1-2.1)**	**2.2 (1.3-4)**
Hyperglycemia	26 (20%)	11 (50%)	**4 (1.3-11)**	**2.4 (1.7-3.6)**
Hiperglucemia	26 (20%)	11 (50%)	**4 (1,3-11)**	**2,4 (1,7-3,6)**

Hyperglycemia: levels above 126 mg/dL in term newborn infants and 180 mg/dL in premature patients. External malformations: it refers to major alterations, such as midline malformations, congenital heart disease and severe cyanosis, head deformities or any other visible malformation involving vital functions.
Alveolar-arterial oxygen gradient: $p(A-a)O_2$.
Alveolar-arterial ratio: pAO_2/paO_2 (pAO_2 or arterial oxygen partial pressure: $(PB-PH_2O) \times FiO_2 - (PaCO_2/0.8) \times 1.25$).
* The dash (-) represents the category of reference.
SA: Silverman Andersen score.

accustomed to similar scales such as the Apgar Score.[31]

The SNAP and SNAPPE scales are the most widely used. In their first version, they included a wide range of outcome measures that complicated their implementation, which led to a re-edition in 2001: SNAP-II and SNAPPE II.[8] The latter, unlike our score, was used in 25 429 newborn infants in four hospital facilities, with an area under the curve of 0.91, excluding newborn infants seen at the NICU.

The second version of CRIB[32] was developed following the release of surfactant use. It included newborn infants admitted at intensive care units,

TABLE 3. *Stratified analysis of the scale scoring: risk, adjusted risk and survival probability*

Outcome measure	Live 183	Dead 44	HR (CI 95%)*	p-value
Prenatal steroids	82 (45%)	17 (39%)	0.7 (0.1-2.5)	0.6
Apgar score at five minutes				
9-10	90 (49%)	6 (13%)	-	
7-8	77 (42%)	22 (50%)	1.3 (0.4-13)	0.3
< 6	16 (9%)	16 (37%)	2.7 (1.4-5.2)	**0.05**
Birthweight (g)				
> 2500	49 (27%)	8 (18%)	-	
1500-2499	86 (47%)	11 (25%)	0.8 (0.4-2)	0.4
< 1499	48 (26%)	25 (56%)	4.7 (1.2-9)	**0.01**
Lactate (mmol/L				
< 1	99 (54%)	3 (7%)	-	
1.1-3.9	38 (21%)	7 (15%)	0.4 (0.1-3)	0.6
> 4	46 (25%)	34 (78%)	5.6 (1.2-7)	**0.03**
a/A				
> 0.6	48 (26%)	2 (5%)	-	
0.59-0.26	16 (9%)	9 (20%)	1.2 (0.7-1.7)	0.07
< 0.25	19 (65%)	33 (75%)	1.8 (0.9-4)	0.06
$P(Ao_2 - aO_2)$				
< 100	9 (5%)	2 (5%)	-	
100-299	165 (90%)	8 (18%)	0.2 (0.01-0.7)	**0.05**
> 300	9 (5%)	34 (77%)	2.5 (1.5-10)	**0.001**
Platelets (cell/µL)				
> 150 000	143 (78%)	5 (12%)	-	
50 000-149 000	35 (19%)	17 (38%)	1.6 (0.4-15)	0.7
< 49 000	5 (3%)	22 (50%)	6.3 (2-17)	**0.001**
Serum glucose (mg/dL)				
< 126	114 (62%)	8 (19%)	-	
127-200	40 (22%)	25 (56%)	2.3 (1.2-6)	**0.05**
> 201	29 (16%)	11 (25%)	1.2 (0.7-13)	0.4
EMN-9 Mex Score				
From 1 to 7	50 (27%)	1 (2%)	-	-
From 8 to 11	80 (44%)	4 (10%)	2.4 (0.2-21)	0.4
From 12 to 15	46 (25%)	22 (50%)	18 (2.4-133)	**0.005**
From 16 to 18	7 (4%)	17 (38%)	85 (11-102)	**< 0.0001**

* The dash (-) represents the category of reference.
HR: hazard ratio.

TABLE 4. *Validity of the Neonatal Mortality Score-9 Mexico divided into four categories*

Score	Sensitivity	Specificity	+PV	-PV	+LR	-LR	AUC
From 1 to 7	2%	73%	2%	76%	0.08 (0.01-0.5)	1.34 (1.22-1.49)	0.50 (0.1-0.7)
From 8 to 11	9%	56%	5%	72%	0.21 (1.3-1.8)	1.6 (1.4-1.7)	0.75 (0.63-0.89)
From 12 to 15	50%	75%	32%	86%	1.9 (1.4-2.8)	0.67 (0.5-0.9)	0.92 (0.88-0.94)
From 16 to 18	40%	99%	71%	90%	10 (4.3-23)	0.6 (0.4-0.8)	0.95 (0.9-0.97)

PV: predictive value.
LR: likelihood ratio.
AUC: area under the curve.

but it is designed for patients weighing less than 1500 g, as against our score that took into account newborns of any weight. The CRIB II has been used in different hospitals and it reported an area under the curve of between 0.86 and 0.9.[33]

A scale developed using a methodology similar to ours was published in Mexico in 2001.[34] However, the newborn infants used to validate the data were gathered from three referral centers of our country where deliveries are not assisted, so the initial approach might have changed the outcome of subjects included in the study. These conditions affect the external validity of that scale; besides, outcome measures as sepsis and heart failure may vary in their identification depending on who rates them. The interpretation of this scale is based on substituting the β coefficient of each outcome measure in the logistic regression formula, a fact that may delay and complicate its implementation in daily clinical practice. It presents an area under the curve of 0.86 and there are no other publications mentioning to have used it or validated it.

The NEOCOSUR Scale that was developed as a result of a multicenter effort in Latin American countries was validated in a population of over 1800 very low weight newborn infants using six prognostic outcome measures (weight, gestational age, Apgar score at one minute, congenital malformations, prenatal use of steroids and maternal age) with an area under the curve of 0.85, with the advantage of being useful for other outcomes besides mortality, such as bronchopulmonary dysplasia and intraventricular hemorrhage.[35] Compared to other scales or scores, it has a stronger mortality predictive power.[8]

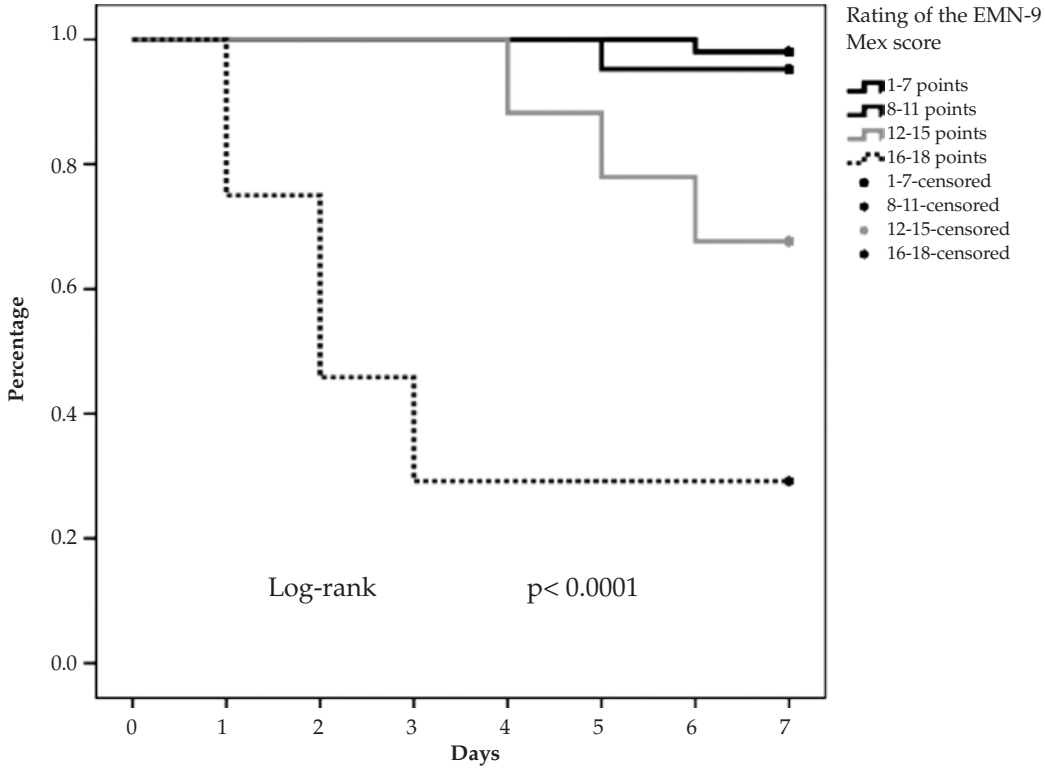
Therefore, the EMN-9 Mex is a mortality predictive scale that is easy to implement and interpret, which can be used in newborn infants regardless of their birth weight, and which introduces other outcome measures that have not been used in other scales or scores.

Its weaknesses lie in the fact that the sample size and the target population are restricted to a single center while treatment approach is limited to the institution´s resources. Newborn infants selected were exclusively seen at the Intensive Care Unit and the prognostic power of our score is limited to mortality in the early neonatal stage.

CONCLUSIONS

The EMN-9 Mex is a novel proposal validated for newborn infants of all weights, supported in outcome measures covering a

FIGURE 2. *Survival curve by category according to the Neonatal Mortality Score-9 Mexico (EMN-9 Mex)*



wide spectrum of diseases that lead to neonatal mortality. It would be worth validating it in a larger neonate population in other hospital facilities to specifically check how effective it is for premature, late premature, term and post-term infants. ■

REFERENCES

1. Shiffman J. Issue attention in global health: the case of newborn survival. *Lancet* 2010;375(9730):2045-9.
2. Oestergaard MZ, Inoue M, Yoshida S, Mahanani WR, et al. Neonatal mortality levels for 193 countries in 2009 with trends since 1990: a systematic analysis of progress, projections, and priorities. *PLoS Med* 2011;8(8):e1001080.
3. Martines J, Paul VK, Bhutta ZA, Koblinsky M, et al. Neonatal survival: a call for action. *Lancet* 2005;365(9465):1189-97.
4. Murguía SM, Lozano R, Santos JI. Mortalidad perinatal por asfixia en México: problema prioritario de salud pública por resolver. *Bol Med Hosp Infant Mex* 2005;62(5):375-83.
5. Záyago-Espinosa M. Utilidad de dos escalas de gravedad como factor de predictivo de mortalidad en neonatos pretérminos. *Rev Sanid Milit Mex* 2006;60(4):243-7.
6. Gagliardi L, Cavazza A, Brunelli A, Battaglioli M, et al. Assessing mortality risk in very low birthweight infants: a comparison of CRIB, CRIB-II, and SNAPPE-II. *Arch Dis Fetal Neonatal Ed* 2004;89(5):F419-22.
7. Maier RF, Rey M, Metze BC, Obladen M. Comparison of mortality risk: a score for very low birthweight infants. *Arch Dis Child Fetal Neonatal Ed* 1997;76(3):F146-50.
8. Marshall G, Tapia JL, D'Apremont I, Grandi C, et al. A new score for predicting neonatal very low birth weight mortality risk in the NEOCOSUR South American Network. *J Perinatol* 2005;25(9):577-82.
9. Aguilar-Barojas S. Fórmulas para el cálculo de la muestra en investigaciones de salud. *Salud en Tabasco 2005;*11(1-2):333-8.
10. Casey BM, Mclntire DD, Leveno KJ. The continuing value of Apgar score for the assessment of newborn infants. *N Eng J Med* 2001;344(7):467-71.
11. Lawn CJ, Weir FJ, McGuire W. Base administration or fluid bolus for preventing morbidity and mortality in preterm infants with metabolic acidosis. *Cochrane Database Syst Rev* 2005;2:CD003215.
12. García HJ, Aparicio-de la Luz S, Franco-Gutiérrez M, González-Lara D, et al. Factores pronósticos de asociados a mortalidad en recién nacidos con hernia diafragmática congénita. *Gac Med Mex* 2003;139(1):7-14.
13. Yasmin S, Osrin D, Paul E, Costello A. Neonatal mortality of low-birth-weight infants in Bangladesh. *Bull World Health Organ* 2001;79(7):608-14.
14. Kao LS, Morris BH, Lally KP, Stewart CD, et al. Hyperglycemia and morbidity and mortality in extremely low birth weight infants. *J Perinatol* 2006;26(12):730-6.
15. Vincent JL, Yagushi A, Pradier O. Platelet function in sepsis. *Crit Care Med* 2002;30(5 Suppl):S313-7.
16. Fernández HG, Vieira AA, Barbosa AD. The correlation between plasma lactate concentrations and early neonatal mortality. *Rev Bras Ter Intensiva* 2012;24(2):184-7.
17. Mathur NB, Garg P, Mishra TK. Predictors of fatality in neonates requiring mechanical ventilation. *Indian Pediatr* 2005;42(7):645-51.
18. Dimitriou G, Fouzas S, Giannakopoulos I, Papadopoulos VG, et al. Prediction of respiratory failure in late-preterm infants with respiratory distress at birth. *Eur J Pediatr* 2011;170(1):45-50.
19. Levit O, Bhandari V, Li FY, Shabanova V, et al. Clinical and laboratory factors that predict death in very low birth weight infants presenting with late-onset sepsis. *Pediatr Infect Dis J* 2014;33(2):143-6.
20. Richardson DK, Corcoran JD, Escobar GJ, Lee SK. SNAP-II and SNAPPE-II: Simplified newborn illness severity and mortality risk scores. *J Pediatr* 2001;138(1):92-100.
21. McCormick MC. The contribution of low birth weight to infant mortality and childhood morbidity. *N Eng J Med* 1985;312(2):82-90.
22. Unterscheider J, O`Donoghue K, Daly S, Geary MP, et al. Fetal growth restriction and the risk of perinatal mortality-case studies from de multicentre PORTO study. *BMC Pregnancy Childbirth* 2014;14:63.
23. Alexander GR, de Caunes F, Hulsey TC, Tompkins ME, et al. Validity of postnatal assessments of gestational age: a comparison of the method of Ballard et al. and early ultrasonography. *Am J Obstet Gynecol* 1992;166(3);891-5.
24. Yau KI, Hsu CH. Factors affecting the mortality of sick newborns admitted to intensive care units. *ActaPaedtr Taiwan* 1999;40(2):75-82.
25. Horbar JD. A calculator program for determining indices of neonatal respiratory distress syndrome severity. *Am J Perinatol* 1987;4(1):20-3.
26. Mendoza-Domínguez S, Zavala-Mendoza A, López-Tamanaja NL, Rodríguez-Zepeda JJ, et al. Índices de oxigenación en recién nacidos en estado crítico. *Rev Mex Pediatr* 1999;66(1):14-7.
27. Varkilova L, Slancheva B, Emilova Z, Nikolov A, et al. Blood lactate measurements as a diagnostic and prognostic tool after birth asphyxia in newborn infants with gestational age > or = 34 gestational weeks. A*kush Ginekol (Sofiia)* 2013;52(3):36-43. Bulgaria.
28. Bauman ME, Cheung PY, Massicotte MP. Hemostasis and platelet dysfunction in asphyxiated neonates. *J Pediatr* 2011;158(2 Suppl):e35-9.
29. Beardsall K, Vanhaesebrouck S, Ogilvy-Stuart AL, Vanhole C, et al. Prevalence and determinants of hyperglycemia in very low birth weight infants: cohort analyses of theNIRTURE study. *J Pediatr* 2010;157(5):715-9.
30. Hirshberg E, Larsen G, Van Duker H. Alterations in glucose homeostasis in the pediatric intensive care unit: Hyperglycemia and glucose variability are associated with increased mortality and morbidity. *Pediatr Crit Care Med* 2008;9(4):361-6.
31. Apgar V. Infant resuscitation. 1957. *Conn Med* 2007;71(9):553-5.
32. Baumer JH, Wright D, Mill T. Illness severity measured by CRIB score: a product of changes in perinatal care? *Arch Dis Child Fetal Neonatal Ed* 1997;77(3):F211-5.
33. Sarquis AL, Miyaki M, Cat MN. Aplicação do escore CRIB para avaliar o risco de mortalidade neonatal. *J Pediatr (Rio J)* 2002;78(3):225-9.
34. García H, Villegas-Silva R, Villanueva-García D, González-Cabello H, et al. Validation of a prognostic index in the critically ill newborn.*RevInvestigClin* 2000;52(4):406-14.
35. Tavosnanska J, Carreras IM, Fariña D, Luchternberg G, et al. Morbimortalidad de recién nacidos con menos de 1500 gramos asistidos en hospitales públicos de la Ciudad de Buenos Aires. *Arch Argent Pediatr* 2012;110(5):394-403.