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ORIGINAL RESEARCH

Proposal of a new predictive model of mortality in high-risk newborns and evaluation of its performance.

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Abstract

Introduction: The aim of this study was to establish a predictive model of mortality in high-risk newborns.

Methods: An epidemiological, observational, and cross-sectional study was carried out at the Isidro Ayora Gynecological Hospital, Quito, Ecuador in 201. The study included 220 high-risk newborns.

Results: No significant associations with prenatal factors were found, but a statistical relationship with weight, gestational age, Appearance, Pulse, Grimace, Activity, and Respiration (APGAR) score, resuscitation needs, and the presence of congenital anomalies in addition to shock, pulmonary hemorrhage, hyperglycemia, acidosis, and hospital stay was noted.

Conclusion: The presence of a more significant base excess, minimum fraction of inspired oxygen (FiO_2), septic shock, and at least one congenital defect with small gestational age determined an 80% probability of death. If the base excess was > –12 mEq/L, the infant was 13 times more likely to die, and if the infant required a minimum FiO_2 > 29%, the newborn was 4.2 times more likely to die. The reliability of the excess base increase predicted a 76.3% higher risk of death.

Keywords: Child mortality; neonatal intensive care unit; Bayesian prediction; fetal growth retardation; congenital defects; shock; Lung diseases; acidosis.

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Introduction

Background/rationale

Prediction models facilitate early identification of critically ill children thus allowing attention toward their referral to a hospital in addition to timely and adequate transport and efficient allocation of resources to anticipate accurate clinical management. Worldwide, several prediction models have been developed to identify children at higher risk of hospitalization, mortality, or clinical deterioration in low- or medium-resource clinical care settings. However, none of them are routinely used in clinical practice. Only a few tools have been externally validated and compared in large prospective cohorts, and these are too heterogeneous among themselves. Limited evidence concerning the validity, reliability, and impact of pediatric early warning scores in resource-limited settings is available. It should be noted that most of the tools were applied to the general pediatric population, and very few have been applied to newborns as we are proposing in this article.

On the other hand, despite advances that have been made to reduce mortality in children, the neonatal component is the one part that has decreased the least over these years since a high percentage of neonatal deaths are potentially reducible, especially prematurity and low birth weight [1]. Timely and adequate detection of neonates at high risk and comprehensive and specialized care will lead to a decrease in neonatal mortality [2]. Regarding prenatal characteristics, it is expected that maternal age is associated with neonatal mortality, that is, adolescent mothers will have preterm infants more frequently than older mothers [3] since their age limits adequate control of pregnancy. This population is not fully mature and presents a higher percentage of infections and premature rupture of membranes and chorioamnionitis all of which are conditions that are associated with higher mortality [4]. It is important to consider that regardless of maternal age, if other complications, such as hypertensive disorders occur, the pregnancy can be interrupted, thus generating health risks for the neonate [5].

In relation to neonatal factors, higher survival is expected in women [6].The relationship between weight and mortality is known. The higher the weight of the neonate, the lower the mortality, the group of extreme premature infants, under 1000 g, stands out as the one with the highest mortality, long hospital stay and large number of comorbidities [7]. The Appearance, Pulse, Grimace, Activity, and Respiration (APGAR) scale is a prognostic factor for neurodevelopment and the success of resuscitation [8], especially at 5 and 10 min of life when it the score is < 6. The score is associated with risk of mortality and is part of a groups of indicators consisting of several mortality scales, such as the Score for Neonatology Physiology with Perinatal Extension and the Clinical Risk Index for Babies (SNAPPE and CRIB, respectively), especially in premature infants [9]. The need for advanced cardiopulmonary resuscitation is also associated with mortality and neurodevelopmental impairment [10, 11]. The early use of surfactant is beneficial for the recovery of a premature baby since it reduces the need for invasive ventilation and long-term complications such as bronchopulmonary dysplasia [12, 13]; association of these factors was expected in our study population.

In addition, major congenital anomalies are determining factors of mortality, a study of 8521 neonates with major anomalies determined that 617 (7.2%) died in the first five years, and of these, half of the deaths occurred in the first week of life, and survival was lower in preterm than in term infants [14]. Critically ill neonates are also expected to present severe comorbidities, such as shock of any etiology and coagulation disorders, which are related to pulmonary hemorrhage, both of which determine up to a 50% probability of dying [15].

Another important element in this group of neonates is metabolic alterations since glucose dysregulation is frequent, which has resulted in a higher prevalence of encephalopathy. Hyperglycemic episodes are associated with deterioration in global brain function and seizures [16]; a systematic review found that episodes of glu-cose dysregulation are associated with death, seizures, intraventricular hemorrhage grades I to IV, leukomalacia, cerebellar hemorrhage, and brain abnormalities as defined by magnetic resonance imaging (MRI) [17]. In addition, acid-base balance disorders are a predictor of mortality in neonates, and metabolic acidosis, which is defined as a low pH and an excess of high base, will determine neurological damage and hypoxyco-ischemic encephalopathy, a risk that begins with a base deficit of

12 mEq/L and/or mixed acidosis with pH (< 7.0) [18]. Regarding the days of hospitalization, especially in the Neonatal Intensive Care Unit (NICU), an association with a higher frequency of comorbidities, higher requirements for blood products, and a higher mortality rate is expected [19].

The objective of this research was to establish a predictive model of mortality in high-risk newborns in the local context.

Population and methods

Study design

The study design was epidemiological, observational, cross-sectional, and analytical with a cohort of patients.

Stage

The project had four stages: (1) identification of high-risk neonates who required hospitalization in the NICU of the "Isidro Ayora" Gyneco-obstetric Hospital (HGOIA), (2) collection of clinical and laboratory variables during their stay in the NICU, (3) bivariate and multivariate analyses of the defined variables, and (4) construction of a mathematical model through logistic regression using the advanced method by Wald to determine predictive variables of mortality with the variables that presented statistical significance in the bivariate analysis. The study was carried out at the HGOIA of the city of Quito during 2019.

Participants

High-risk infants admitted to the HGOIA NICU were included. The inclusion criteria consisted of several parameters: (1) neonatal patients who were admitted to the NICU, (2) aged < 28 days, (3) both sexes, (4) any ethnic group, and (5) in critical condition requiring intensive care due to hemodynamic instability and moderate to severe respiratory distress. The exclusion criteria were patients who were > 28 days upon admission and in intermediate conditions. Exclusion criteria in all cohorts consisted of patients with incomplete information or those who were transferred.

Variables

The dependent variable was mortality. Descriptive variables were newborn sex, maternal age, previous abortions, use of prenatal steroids, multiple pregnancies, maternal perinatal infections, premature rupture of membranes, maternal chorioamnionitis, gestational diabetes, and hypertensive disorders of pregnancy. Independent variables were small for gestational age, presence of congenital anomalies, septic shock, base excess, and fraction of inspired oxygen (FiO_2). For the analytical study, two groups were formed: (1) non-survivors/ de-ceased and (2) survivors.

Data/Measurement Sources

Clinical information and complementary examinations were collected from the medical records of critically ill infants in addition to a detailed physical examination of each patient.

Control of sources of bias.

The units of measurement were precisely delimited for each variable analyzed, and information was only included during the patient's stay in the NICU, except for the number of days of hospitalization in an intermediate care unit. The information was collected by a single researcher.

Study size

The sample was non-probabilistic in which all potentially eligible hospital cases were included based on the cases admitted to the NICU during 2019. The sample size consisted of 220 patients.

Statistical Methods

The quantitative variables in scale are presented with means and standard deviations. Nominal quantitative variables are presented as frequencies and percentages. The statistical program SPSS ©, (IBM Corp, Released 2013. Windows, Version 22.0. Armonk, NY, USA) was used. For the bivariate and multivariate analyses of categorical and quantitative variables, a logistic regression was subsequently performed using the Wald "Advance by Steps" method, which determined that the predictive variables of mortality considered the variables that were statistically significant in the bivariate analysis. Odds ratio (OR) and confidence intervals (CI) were reported with the corresponding P values.

Results

Participants

Table 1 shows the distribution of prenatal characteristics with a mean maternal age of 27.7 years. A representative percentage of mothers in borderline ages was not established, and no statistical association was found with abortions, use of prenatal steroids, multiple pregnancies, perinatal infections, chorioamnionitis, and/or diabetes. Only 30% of the patients had some pregnancy-associated hypertensive disorder. Regarding prenatal factors, no statistically significant association was found.

Table 2 shows the neonatal characteristics. The mean weight was 1582 g and was significantly related to mortality. Differences in the means of the weights were determined with a P= 0.004 with mean values of 1478.5 g in non-survivors versus 1650.2 g in survivors. The average gestational age associated with mortality (survivors versus non-survivors) was 32.3 weeks (P= 0.048) with a mean of 31.6 weeks in de-ceased versus 32.6 weeks in survivors. About half (58.6%) of the neonates had low weight for their gestational ages, which showed a significant association with mortality (P = 0.005), and the proportion of non-survivors was 47.29% in the neonates with low weight versus 28.57% in those with adequate weight. Thus, neonates with growth restriction were 2.24 times more likely to die.

The APGAR scale at one min post-birth was 6, which was statistically significant (P < 0.0001) with respect to a mean of a score of 6 in non-survivors versus 7 in survivors. On the APGAR at 5 min, a mean of 8 was obtained that was associated with mortality (P = 0.039) with a mean of 7 in non-survivors versus 8 in survivors. Less than half (46.3%) of the neonates required advanced resuscitation with statistically significant differences (P < 0.0001), and the proportion of non-survivors who required resuscitation was 53.47% versus 28.21% in those who did not require it. The neonates who required advanced CPR were 2.93 times more likely not to survive.

Table 1 Data with general descriptions of the group

Prenatal characteristics	Total	Discharge condition		P	OR (CI-95%)
		Non-survivor	Survivor		
Edad (media (años))[1] años	27.77(±7.24)	27.62 (±7.73)	27.87 (±6.94)	-	-
Previous abortions (n(%))[2]					
No abortions	166 (75.45)	71 (42.77)	95 (57.23)		
One	36 (16.36)	9 (25.00)	27 (75.00)	0.141	-
Two or more	18 (8.18)	7 (38.89)	11 (61.11)		
Prenatal steroids (n(%))[2]					
Yes	120 (55.05)	43 (35.83)	77 (64.17)	0.174	0.69 (0.40-1.18)
No	98 (44.95)	44 (44.90)	54 (55.10)		
Multiple pregnancy (n(%))[2]					
Yes	40 (18.18)	15 (37.50)	25 (62.50)	0.770	0.99 (0.44-1.82)
No	180 (81.82)	72 (40.00)	108 (60.00)		
Peripartum maternal infections (n(%))[2]					
Yes	93 (42.47)	33 (35.48)	60 (64.52)	0.270	0.73 (0.42-1.27)
No	126 (57.53)	54 (42.86)	72 (57.14)		
Premature rupture of membranes (n(%))[2]					
Yes	39 (17.81)	17 (43.59)	22 (56.41)	0.587	1.21 (0.60-2.45)
No	180 (82.19)	70 (38.89)	110 (61.11)		
Maternal chorioamnionitis (n(%))[2]					
Yes	36 (16.36)	17 (47.22)	19 (52.78)	0.303	1.46 (0.71-2.99)
No	184 (83.64)	70 (38.04)	114 (61.96)		
Gestational diabetes (n(%))[2]					
Yes	25 (11.42)	13 (52.00)	12 (48.00)	1.660	0.79 (0.79-4.15)
No	194 (88.58)	73 (37.63)	121 (62.37)		
Hypertensive disorders of pregnancy (n(%))[2]					
Yes	68 (30.91)	27 (39.71)	41 (60.29)	0.974	1.01 (0.56-1.81)
No	152 (69.09)	60 (39.47)	92 (60.53)		

SD = Standard Deviation; based on the Mann-Whitney test of independent samples, 2 / = based on the chi-square test for statistical homogeneity.

Prophylactic surfactant was used in 51.6% of neonates with no significant differences in relation to prognosis. About one-quarter (21.36%) of neonates presented congenital anomalies with a significant difference of $P = 0.002$. Non-survivors and survivors with anomalies were 59.5% and 34.1%, respectively that is, neonates with congenital anomalies were 2.85 times more likely to die.

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Table 3 shows that the main admission diagnoses were prematurity (86.8%) and hyaline membrane disease (HMI) in 76.3%. The most severe comorbidities and greatest possibility of a fatal outcome was septic shock in 18.1% with significant differences ($P = 0.0001$) between the proportion of non-survivors with septic shock (75%) and 25% who survived septic shock, indicating that if a neonate presents septic shock, they were 6.47 times more likely to die.

Another severe comorbidity was pulmonary hemorrhage. Infants with pulmonary hemorrhage who did not survive constituted 90.6% versus 9.3% who did survive ($P = 0.0001$), indicating that a neonate with pulmonary hemorrhage is 21 times more likely to die. In addition, 100 neonates had intraventricular hemorrhage (IVH) with significant differences in non-survivors and survivors ($P = 0.009$); 14.58% of neonates with HIV grade I, 27.27% with HIV grade II, 50% with HIV grade III, and 50% with HIV grade IV died, indicating that the increase in HIV severity also caused an increase in mortality.

Other significant differences when comparing the means between non-survivors and survivors ($P < 0.05$) were also found: (1) higher glycemia, 213 mg/dL in non-survivors versus 159 mg/dL in survivors, (2) minimum mean arterial pressure 26 mmHg in non-survivors versus 30 mmHg in survivors, (3) the lowest temperature presented during the stay in the NICU was 35.60 ° C in non-survivors versus 35.90 ° C in survivors,

Table 2 Distribution of natal characteristics in relation to discharge condition

Natal characteristics	Total	Discharge condition		*P*	OR (CI-95%)
		Non-survivor	Survivor		
Weight (mean (SD))[1/] gr	1.582.35 (±735.7)	1.478.51 (±843.55)	1.650.27 (±650.11)	0.004*	-
Gestacional age (mean (SD))[1/]	32.33 (±3.61)	31.86 (±4.26)	32.64 (±3.08)	0.048*	-
Apgar 1 minute (mean (SD))[1/]	6 (±2)	6 (±2)	7 (±2)	<0.0001*	-
Apgar 5 minute (mean (SD))[1/]	8 (±1)	7 (±2)	8 (±1)	0.039*	-
Sex (n(%))[2/]					
Male	131 (59.55)	54 (41.22)	77 (58.78)	0.537*	1.19 (0.68-2.07)
Female	89 (40.45)	33 (37.08)	56 (62.92)		
Low weight for gestational age (n(%))[2/]					
Yes	129 (58.64)	61 (47.29)	68 (52.71)	0.005**	2.24***(1.27-3.97)
No	91 (41.36)	26 (28.57)	65 (71.43)		
Advanced resuscitation needs (n(%))[2/]					
Yes	101 (46.33)	54 (53.47)	47 (46.53)	<0.0001**	2.93***(1.67-5.13)
No	117 (53.67)	33 (28.21)	84 (71.79)		
Use of surfactant in the 1st hour of life (n(%))[2/]					
Yes	113 (51.60)	48 (42.48)	65 (57.52)	0.390	1.27 (0.74-2.18)
No	106 (48.40)	39 (36.79)	67 (63.21)		
Congenital abnormalities (n(%))[2/]					
Yes	47 (21.36)	28 (59.57)	19 (40.43)	0.002**	2.85***(1.47-5.52)
No	173 (78.64)	59 (34.10)	114 (65.90)		

Note: SD = Standard Deviation; 1 / = based on the Mann-Whitney test of independent samples * significant differences in the mean between non-survivors and survivors ;, 2 / = based on the chi-square test for statistical homogeneity ** significant differences in the proportion of non-survivors; *** risk factor for mortality

Table 3 Postnatal characteristics of the patients and their relationship with the discharge condition.

Postnatal characteristics	Total	Discharge condition		*P*
		Non-survivor	Survivor	
Admission diagnosis (n(%))[2/]	*Prematurity*			
Yes	191 (86.82%)	71 (37.17%)	120 (62.83%)	0.065
No	29 (13.18%)	16 (55.17%)	13 (44.83%)	
	EMH			
Yes	168 (76.36%)	62 (36.90%)	106 (63.01%)	0.150
No	52 (23.64%)	25 (48.08%)	27 (51.92%)	
	Ethnicity (n(%))[2/]			
Hispanic	213 (96.82%)	86 (40.38%)	127 (59.62%)	
Afro-descendant	6 (2.73%)	1 (16.67%)	5 (83.33%)	0.363
Shuar	1 (0.45%)	0 (0)	1 (100%)	
Comorbidities (n(%))[2/]	Septic shock			
Yes	40 (18.18)	30 (75.00)	10 (25.00)	<0.001**
No	180 (81.82)	57 (31.67)	123 (68.33)	
	Pulmonary hemorrhage			
Yes	32 (14.55)	29 (90.63)	3 (9.38)	<0.001**
No	188 (85.45)	58 (30.85)	130 (69.15)	
	Intraventricular hemorrhage (n (%))[2/]			
Grade I	48 (48.00)	7 (14.58)	41 (85.42)	0.009**
Grade II	22 (22.00)	6 (27.27)	16 (72.73)	
Grade III	14 (14.00)	7 (50.00)	7 (50.00)	
Grade IV	16 (16.00)	8 (50.00)	8 (50.00)	
Lowest blood glucose (mean (SD)) [1/] [mg/dl]	49.31 (±22.48)	49.11 (±28.35)	49.44 (±17.74)	0.257
Highest glycemia (mean (SD)) [1/] [mg/dl]	179.85(±101.79)	212.99 (±118.34)	159.17 (±84.01)	<0.001*
Lower MAP (mean (SD)) [1/][mmHg]	28.82 (±8.35)	26.03 (±9.07)	30.64 (±7.33)	<0.001*
Lower temperature (mean (SD))[1/][°C]	35.84 (±0.78)	35.64 (±1.06)	35.97 (±0.49)	0.013*
Lower urinary output (mean (SD))[1/][ml/kg/h]	3.51 (±14.04)	2.35 (±1.36)	4.26 (±18.01)	0.080
Lower platetes (mean (SD))[1/][u/uL]	129.890 (84990)	95.068 (±69.913)	152.669 (86.473)	<0.001*
Oxygenation index (mean (SD))[1/]	0.72 (±0.69)	0.63 (±1.03)	0.78 (±0.31)	<0.001*
IMV days (mean (SD)) [1/]	13.42 (±19.53)	16.33 (±24.32)	11.5 (±15.39)	0.260
NMV days (mean (SD))[1/]	8.06 (±9.52)	8.13 (±12.26)	8.05 (±8.63)	0.018*
Lower serum pH (mean (SD))[1/]	7.18 (±1.23)	6.97 (±0.20)	7.32 (±1.56)	0.040*
Highest pCO_2 (mean (SD))[1/][mmHg]	60.18 (±23.21)	69.1 (±29.96)	54.35 (±14.89)	<0.001*
Lower pCO_2 (mean (SD))[1/][mmHg]	23.43 (±7.68)	23.01 (±8.47)	23.71 (±7.13)	0.148
Maximum excess of bases (mean (SD))[1/]	-14.21 (±7.97)	-19 (±8.54)	-11.08 (±5.74)	<0.001*
Highest lactate (mean (SD))[1/][mmol/L]	9.1 (±6.64)	13.04 (±7.09)	6.52 (±4.85)	<0.001*
Lowest Anion Gap (mean (SD))[1/][mmol/L]	12 (±7.97)	13.21 (±4.88)	11.21 (±9.39)	<0.001*
Highest Anion Gap (mean (SD))[1/][mmol/L]	20.58 (±7.89)	23.6 (±9.74)	18.6 (±5.61)	<0.001*
Minimum FiO_2 (mean (SD))[1/][mmHg]	33.36 (±14.68)	40.25 (±18.58)	28.85 (±8.99)	<0.001*
Maximum FiO_2 (mean (SD))[1/][mmmHg]	74.3 ± (23.55)	88.87(17.81)	64.77 (±21.96)	<0.001*
Minimum Hemoglobin value (mean (SD))[1/][g/dL]	12.05 (±3.06)	11.9 (±3.26)	12.15 (±2.93)	0.402
Blood products (mean (SD))[1/]	6.64 (±7.99)	8.66 (±9)	5.32 (±6.99)	<0.001*
NICU hospitalization days (mean (SD))[1/]	21.32 (±23.55)	20.17 (±26.23)	22.07 (±21.68)	0.021*
Intermediate cate hospitalization days (mean (SD))[1/]	10.99 (±11.31)	2.2 (±7.26)	16.83 (±9.62)	<0.001*
Total days of hospitalization (mean (SD))[1/]	32.38 (±27.21)	22.33 (±26.87)	38.95 (±25.45)	<0.001*

Note: SD = Standard Deviation; 1 / = based on the Mann-Whitney test of independent samples * significant differences in the mean between non-survivors and survivors ;, 2 / = based on the chi-square test for statistical homogeneity ** significant differences -effective in the proportion of non-survivors; IMV: Invasive mechanical ventilation. NMV: noninvasive mechanical ventilation.

(4) the lowest platelet determination was 95,068 platelets/mm3 in non-survivors versus 152,669 platelets/mm3 in survivors, group of non-survivors vs 5.32 in survivors. (5) non-invasive mechanical ventilation (NIMV) days were 8.1 in non-survivors versus 8 in survivors, (6) with respect to acid-base balance, lower serum pH 6.97 (0.20) was found in non-survivors versus 7.32 (1.56) in survivors with a $P = 0.040$, (7) the highest pCO_2 was 69.10 mmHg in non-survivors versus 54.35 mmHg in survivors, (8) the highest base excess was –19

mEq/L in non-survivors versus –11.08 mEq / L in survivors, (9) the highest lactate was 13 in non-survivors versus 6 in survivors, (10) the lowest Gap anion 13.2 mmol / L in non-survivors vs 11.2 mmol / L in survivors and the highest Gap anion 23.6 mmol / L in non-survivors vs 18.6 mmol / L in survivors, the minimum inspiratory oxygen fraction (FiO_2) required was 40% in non-survivors vs 28% in survivors and the maximum FiO_2 required 88% in non-survivors vs 64% in survivors. Blood products were used 8.6 times in neonates in the group of non-survivors vs 5.32 in survivors.

The days of hospitalization in the NICU were 20.1 days in non-survivors versus 22 days in survivors, and in intermediate care 2.2 days in non-survivors versus 16.8 days in survivors. The hospital stay was 22.3 days in non-survivors versus 38.9 days in survivors. The general means of the parameters that did not show significance when comparing according to the discharge condition were lower glycemia 49.3 mg / dL, the lowest urinary output 3.5 ml/Kg/h, days of invasive ventilation 13.4 days, and lowest pCO_2 was 23.43 mmHg , hemoglobin 12.5 g/dL

Bivariate analysis

Table 4 shows the logistic regression that determined the predictive variables of mortality, which were small for gestational age, congenital anomalies, septic shock, high base excess, and minimum requirements of in-spired fraction of O_2 (FiO_2) with P <0.05. They were predictors of mortality. The regression model reached 80% accuracy for mortality prediction.

Table 4 Logistic regression model to predict mortality in high-risk neonates

Variables	B	Wald	*P*	OR	CI-OR 95%		Correct classification
					Lower	Upper	
Small for gestational age (yes)	1.48	11.2304	0.008*	4.41	1.85	10.52	80%
Congenital anomalies (yes)	1.28	9.30853	0.002*	3.60	1.58	8.19	
Septic shock (yes)	1.56	10.8578	0.001*	4.76	1.88	12.04	
Higher base excess	0.13	22.685	<0.001	1.14	1.08	1.21	
Minimum FiO_2 required	0.06	11.5897	<0.001*	1.06	1.02	1.09	
Constant	-5.71	49.744	<0.001*				

Note: Based on the chi-square test; * significant variable *P*-value <0.05, ** OR = significant odds ratio; based on Logistic Regression Method = Step Forward (Wald).

Multivariate analysis

The multivariate relationship of the model produced several results: (1) infants with low weight for gestational age were 4.41 times more likely to die, (2) if they present major congenital anomalies, they were 3.6 times more likely not to survive, (3) when septic shock was associated, they were 4.76 times more likely to die, and (4) if they presented high base excess ranging from –12 mmol/L with an average –19 mmol/L (8.54) for non-survivors and –11.08 (5.7) for survivors and requiring minimum FiO_2 values ranging from 27% to > 40.2% (18.5) in non-survivors and 28.85% (8.99) in survivors, indicating the greater the excess of base and the greater the FiO_2 requirement, the greater the probability of dying.

Table 5 shows the predictive variables of mortality, considering that if the patient had a high base excess (from –12 mEq/L and greater), they had a 73% probability of dying. Administration of FiO_2 > 29% was also a risk for dying. As a minimum requirement, the risk of dying due to the association of these two parameters was 76.3%, and if the presence of congenital anomalies is added, the risk increased to 77.7%. When presenting four conditions, an association with septic shock caused an increase in the probability of dying to 79%, and finally if a neonate was also underweight for his/her gestational age, an 80% chance of dying is present. The mathematical model is shown below:

$$Probability\,(X = death) = \frac{1}{1 + e^{-(-5.71+1.48x_1+1.28x_2+1.56x_3+0.13x_4+0.06x_5)}}$$

Where: e = Exponent, x_1 = Small for gestational age (yes), x_2 = Congenital abnormalities (yes), x_3 = Septic

shock (yes), x_4 = Maximum excess of bases, x_5 = Minimum FiO_2

Sensitivity tests

Table 6 and shows the test for the area of the receiver operating characteristic (ROC) curve (Figure 1) used to predict mortality by means of maximum base excess and minimum FiO_2. Using the ROC curve, we proceeded to determine the cut-off points to predict mortality using excess of base and minimum requirement of FiO_2, as the variables, which were significant in the logistic regression. The point estimate of the area under the curve for the highest excess of bases and minimum requirement of FiO_2 were 0.803 and 0.724, respectively. Since the confidence intervals did not contain the value 0.5, we could confirm that the area under the ROC curve was significantly greater than the minimum. The cut-off point obtained using the Youden index yielded a value of high base excess of –12 mEq/L with a sensitivity of 83%, specificity of 71%, with a 13-fold risk of not surviving. For the minimum FiO_2 requirement, the point was 29% with a sensitivity of 70% and a specificity of 65% with a 4.29-fold risk of not surviving when a minimum $FiO_2 \geq 29\%$ is required. For example, if we have a neonate of 1300 g at 34 weeks gestational age with low birth weight and gastroschisis, and septic shock during his stay in the NICU with metabolic acidosis and an excess of base –18 mmol/L, who required 45% FiO_2 from the start of ventilation, the risk of dying secondary to his condition was 80%

Discusión

Important results

The main finding of the present study was the possibility of predicting mortality in a group of high-risk newborn patients based on five clinically significant variables: (1) weight for gestational age, (2) presence of congenital anomalies, (3) presence of shock septic, (4) measurement of excess base, and (5) requirement for FiO_2. This prediction adequately classified 80% of the cases as belonging to group one (deceased) and group two (survivors). The performance of the score depended on the number of variables that were concurrently analyzed.

In Table 1, no significant association was found between maternal age and survival of high-risk neonates, and a representative percentage of mothers with ages at risk (< 20 years or > 34 years) was not determined, the reported mean age was 27.7 years.

Table 5 Variables distribution according to the Logistic Regression. According to the Advance in Steps (Wald) method

Variables	Correct classification
Variable 1:	73.18%
Higher base excess	
Variable 1+2	
Higher base excess	76.36%
Minimum FiO_2 required	
Variable 1+2+3	
Higher base excess	
Minimum FiO_2	77.73%
Septic shock (Yes)	
Variable 1+2+3+4	
Higher base excess	
Minimum FiO_2	79.09%
Septic shock (Yes)	
Congenital anomalies (Yes)	
Variable 1+2+3+4+5	
Higher base excess	
Minimum FiO_2	80%
Septic shock (Yes)	
Congenital anomalies (Yes)	
Small for gestational age (Yes)	

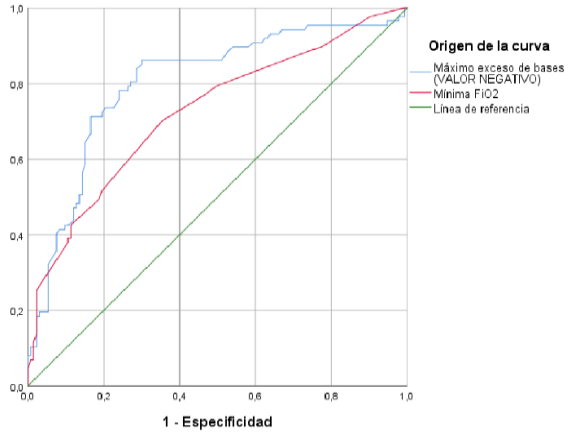

Fig. 1 ROC curve to predict mortality through maximum base excess and minimum required FiO_2.

In addition, the use of prenatal steroids was expected to be a protective factor; however, only 55% of the mothers achieved maturation because they did not receive adequate prenatal care. No difference in the survival of these patients was noted since inadequate is not a widespread practice. Currently, an increase in

multiple pregnancies, due to the use of assisted reproductive techniques exists; however, in our population, only 4% of pregnancies were multiple with no differences in neonatal survival. Infectious complications associated with hypertensive or metabolic disorders, such as gestational diabetes, have been described as causing an increase in neonatal mortality, but in our population, < 40% of patients presented these pathologies because these maternal comorbidities were associated with extreme ages and did not occur in our study population.

Regarding neonatal characteristics, it can be observed in Table 2 that differences were expected in the sex of the neonates with a greater number of male neonates and a greater survival in females, however, the distribution was similar; 59% were men, of which 41% died compared to 41% of women of which 37% died although no statistical differences were noted because the sample was limited. It should be noted that weight determined survival, and extreme prematurity was associated with a notable increase in mortality. In this population, the average weight was 1582 g with 30.3% extremely premature babies who had significant with mortality. The lower the gestational age was, the higher the mortality. The average was 32 weeks with a significant difference in the discharge condition, which was determined above all by the low weight for the gestational age, a factor that is a predictor of mortality.

On the other hand, a low score on the APGAR scale within the first minute post-birth was associated with mortality, and at 5 min, it presented a smaller difference in the outcome, a relationship that can be explained because advanced resuscitation was already administered at 5 min with an appropriate response. Thus, the need for advanced resuscitation determines differences in the discharge condition. Likewise, the use of surfactant caused a reduction in mortality in premature infants. In the study population, only 51% received surfactant during the first hour of life, a factor that did not determine a relationship with mortality, probably because it was a limited sample. Equally important, 21% of our patients had major congenital anomalies, which was determined to be a variable with a statistically significant association with mortality. This factor actually predicted survival in high-risk patients.

Thus, Table 3 shows that 86% of neonates were premature, a factor that was not associated with the out-come, probably because the ranges of prematurity were not differentiated.

Table 6 Test for the area of the ROC curve to predict mortality by means of maximum excess of bases and minimum FiO_2

Curve parameters	Variables	
	Higher base excess (negative value)	Minimum FiO_2 required
Area	0.803	0.724
P-value[1/]	<0.001*	<0.001*
CI-95%	0.74-0.87	0.65-0.79
Cut point	12	29
Sensitivity	83%	70%
Specificity	71%	65%
Reliability	76.36%	66.82%
Negative LR	0.24	0.46
Positive LR	2.86	2.00
OR (CI-95%)	13 (6.62-27.97)	4.29 (2.40-7.67)
Pretest probability	39.55%	39.55%
Post-test probability	65.16%	56.71%

Note: 1/ Null hypothesis: true area = 0.5; *statistical significance $H_0 \neq 0.05$. LR: likelihood ratio

The highly lethal comorbidities that were related to mortality were septic shock and pulmonary hemorrhage; regarding shock, it was the most frequent complication involved in the most different pathologies upon ad-mission of newborns to the NICU, including sepsis. Only 24% had positive blood cultures and an antibiogram, which restricted the appropriate use of antimicrobials. In relation to pulmonary hemorrhage, 90% of these patients died since, at present, it continues to be a pathology that is difficult to manage and has very limited therapeutic options. Additionally, the frequency of intraventricular hemorrhage was a factor associated with discharge condition, greater severity of hemorrhage, greater mortality, a relationship that was deter-mined by extreme prematurity and its association with severe pathologies and long hospital stays.

It is necessary to emphasize that adequate metabolic control determines the outcome of a high-risk neonate, a situation evaluated by the regulation of glycemia. Hyperglycemia was associated with mortality, and values of 179.85 (101.79) mg/dL determined neurological alterations. Currently, it has been shown

that hyperglycemia, rather than episodes of hypoglycemia, is associated with neurodevelopmental disorders as de-scribed a few years ago. Similarly, hypotension was expected to determine the outcome in critical neonates; despite this, hypotension was not an associated factor since the values were generalized regardless of gestational age and days of postnatal life. On the contrary, other more specific evaluations, derived from functional echocardiography and related to cerebral perfusion, which were more reliable indicators of the hemodynamic status of a neonate, were not analyzed. Regarding hypothermia, it was a factor associated with survival.

Concerning hospital stay, an association between the days of hospitalization in the NICU and in intermediate care was found. The stay in intermediate care was a protective factor since the shorter the stay in inter-mediate care was, the lower the mortality. A similar finding with the days of mechanical ventilation were observed since there was a greater association with non-invasive ventilation, establishing that patients who required fewer days of invasive ventilation had a higher survival rate and a lower risk of long-stay complications. Similarly, hypercapnia was associated with mortality. A mean values of 69 mm Hg in the group that died was found, a condition that was associated with failure of conventional ventilation and required more advanced ventilation strategies, which, unfortunately, were limited in our environment.

Regarding the need for oxygen, an association with mortality, especially with the minimum requirements of FIO_2 during treatment in the NICU was found. It was determined that when FIO_2 was > 29%, it established the discharge condition, a situation that reflected severe complications during ventilation and derived from the basic condition of neonates. Regarding the need for blood products, this need was also associated with mortality as it is related to conditions, such as extreme prematurity, bleeding complications, and a long stay in the NICU. It was necessary to analyze metabolic acidosis and its relationship with mortality; the lower the pH was, the higher the mortality. A pH of 6.97 in non-survivors versus a pH of 7.32 in survivors were found, a condition that was ratified by the anion gap value, which also presented a significant relationship. It is noteworthy that the main determinant of mortality was base excess since values > –12 mEq/L predict mortality; therefore, these values should be considered as an early determinant that requires action more aggressive therapies during treatment regardless of the pH value and bicarbonate level, which on occasion, do not present severe modifications. In Table 4, the factors associated with mortality showed that it is relevant that low weight for gestational age was associated with prenatal conditions, such as chronic hypoxia, placental insufficiency, and an intrauterine environment that did not favor the adequate development of the neonate. Low weight became a predictor of mortality if it presented in conjunction with major congenital anomalies. The response to adequate intensive care was limited, and it was shown to be associated with complex complications that were related to sepsis and disseminated intravascular coagulation, such as septic shock and pulmonary hemorrhage. An adequate acid–base balance must be evaluated early based on excess base, a condition that requires early therapy to influence the outcome of a high-risk neonate.

Limitations

The randomization of patients always has a risk of bias, and the probability of expanding the study population and including other health institutions with different social conditions will allow this study and its conclusions to be extrapolated to the general population.

Generalization

Several predictive factors of mortality that were established in this research are included in predictive scales of mortality, which shows that they are results that can be generalized; however, the contribution of new associated variables must be studied in a larger population in order to extend this model to other countries..

Conclusions

The presence of a greater excess of base, minimum FiO_2, septic shock, and at least one congenital defect combined with small for gestational age appears to determine an 80% probability of death. If the base excess is > –12 mEq/L, the infant was 13 times more likely to die, and if the infant required a minimum FiO_2 of > 29%, he/she would be 4.2 times more likely to die. The reliability of the excess base increase predicted a 76.3% higher risk of death, and the high need for FiO_2 predicted a 66.8% higher risk of death. Receiving early

treatment will modify the outcomes in high-risk neonates.

Abbreviations

NICU. Neonatal intensive care unit. HGOIA. Isidro Ayora Gyneco-Obstetric Hospital.

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Authors' contributions

Conceptualization, data curation, formal analysis, fund acquisition, research, resources, software, writing - original draft, validation, visualization, methodology, project management, writing: review and editing were performed by all authors. They contributed in the same way throughout the process. The corresponding author represents the group of authors. All authors read and approved the final version of the manuscript.

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Availability of data and materials

The data sets generated and / or analyzed during the current study are not publicly available due to the confidentiality of the participants, but are available through the corresponding author upon reasonable academic request.

Ethical statements

Institutional Review Committee (IRB) approval: the research was authorized by the CEISH of the "San Francisco de Quito" University in July 2019, with code 2019-052TPG, review report IR-EXP25-2019-CEISH-USFQ.

Protection of people

The authors declare that the procedures followed were in accordance with the ethical standards of the responsible human experimentation committee and in accordance with the World Medical Association and the Singapore Declaration.

Data confidentiality

The authors declares that they have followed the protocols of her workplace regarding the publication of patient data without identification.

Publication consent

The authors have obtained the informed consent of the guardians of the patients and the respective assent. This document is in the possession of the corresponding author. The authorization for the publication of this article has been signed by the guardians or parents.

Conflicts of interest

The authors declare not to have any interest conflicts.

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