Neonatal mortality in intensive care units of Central Brazil

Mortalidade neonatal em unidades de cuidados intensivos no Brasil Central

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Keywords
Infant mortality. Intensive care units, neonatal. Infant, low birth weight. Information systems. Mortality rate.

Abstract

Objective
To identify potential prognostic factors for neonatal mortality among newborns referred to intensive care units.
Methods
A live-birth cohort study was carried out in Goiânia, Central Brazil, from November 1999 to October 2000. Linked birth and infant death certificates were used to ascertain the cohort of live born infants. An additional active surveillance system of neonatal-based mortality was implemented. Exposure variables were collected from birth and death certificates. The outcome was survivors (n=713) and deaths (n=162) in all intensive care units in the study period. Cox's proportional hazards model was applied and a Receiver Operating Characteristic curve was used to compare the performance of statistically significant variables in the multivariable model. Adjusted mortality rates by birth weight and 5-min Apgar score were calculated for each intensive care unit.
Results
Low birth weight and 5-min Apgar score remained independently associated to death. Birth weight equal to 2,500g had 0.71 accuracy (95% CI: 0.65-0.77) for predicting neonatal death (sensitivity =72.2%). A wide variation in the mortality rates was found among intensive care units (9.5-48.1%) and two of them remained with significant high mortality rates even after adjusting for birth weight and 5-min Apgar score.
Conclusions
This study corroborates birth weight as a sensitive screening variable in surveillance programs for neonatal death and also to target intensive care units with high mortality rates for implementing preventive actions and interventions during the delivery period.

Descritores
Mortalidade infantil. Unidades de terapia intensiva neonatal. Recém-nascido de baixo peso. Sistemas de informação. Coeficiente de mortalidade.

Resumo

Objetivo
Identificar fatores prognósticos de mortalidade neonatal em unidades de cuidados intensivos.
Métodos
Realizou-se estudo de coorte de nascidos vivos do município de Goiânia, no período de novembro de 1999 a outubro de 2000. Procedeu-se à vinculação das bases de dados das declarações de nascidos vivos e de óbitos, das quais as variáveis de exposição foram extraídas. Adicionalmente, foi implementado um sistema ativo de

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vigilância de mortalidade neonatal. A variável de efeito foi constituída dos recém-nascidos admitidos nas unidades de cuidados intensivos que sobreviveram (n=713) e dos que morreram (n=162). Utilizou-se o modelo de regressão de Cox para identificar fatores associados à mortalidade neonatal e a curva Receiver Operating Characteristic *para avaliar a acurácia de variáveis estatisticamente significantes em modelo multivariado. Taxas de mortalidade ajustadas por peso de nascimento e Apgar do quinto minuto foram calculadas para cada unidade de cuidados intensivos.*

Resultados

Baixo peso ao nascer e Apgar do quinto minuto permaneceram associados ao óbito neonatal, de forma independente. Peso ao nascer igual a 2.500 g apresentou acurácia de 0,71 (IC 95%: 0,65-0,77) na predição de óbito neonatal (sensibilidade =72,2%). Observou-se ampla variação nas taxas de mortalidade entre as unidades de cuidados intensivos (9,5%-48,1%) sendo que duas delas permaneceram com taxas significantemente mais altas após o ajuste da mortalidade pelo peso de nascimento e Apgar.

Conclusões

Os resultados mostraram que o peso de nascimento é uma variável sensível para uso em triagens em programas de vigilância de óbito neonatal e pode identificar as unidades de cuidados intensivos com altas taxas de mortalidade para implementação de ações preventivas e para intervenções no período intra-parto.

INTRODUCTION

Most of the annual four million neonatal deaths occur in developing countries. A recent literature review comprising 42 countries, which correspond to 90% of all deaths in children under five worldwide, showed the highest rates (33%) were caused by neonatal disorders in 2000, making reduction of neonatal death a global priority.[8] Brazil has one of the highest childhood mortality rates in Latin America. Actions developed to promote infant health, such as mass immunization campaigns, diarrhea prevention and breastfeeding promotion programs, have had a great impact in the post neonatal component of infant mortality. Therefore, infant mortality rates reflect mainly the burden of neonatal mortality in the country. A considerable share of these deaths results from avoidable causes, which means that interventions could have been effective. However, reducing neonatal mortality is hindered by the complex and close relationship between biological and social factors, and by the coverage and quality of health services during prenatal care, delivery and neonatal period.[19]

At present, there is no official surveillance program for high-risk newborns in Brazil, although some municipalities have developed independent programs based on a large number of variables. However, a program based on a combination of several risk factors may not be feasible in the routine practice of health services.[4] Indexes such as the Clinical Risk Index for Babies (CRIB) and Score for Neonatal Acute Physiology (SNAP)[23] have been used to ascertain death prognostic factors in neonatal intensive care units (NICU) settings. Such indexes are somewhat complex to be applied routinely in public health services for surveillance of neonatal mortality. Also, differences in neonatal mortality may occur as a result of the variability in the quality of care provided in private and public settings,[2] with or without NICU.

The Brazilian system of live births information (SINASC) national database has improved substantially in recent years achieving high coverage as well as good reliability.[14,20] Thus, SINASC has been linked with the mortality information system (SIM) to assess variables related to neonatal death.[1,15]

The cost-effectiveness of preventive programs in developing areas should be maximized, and there should be a continuous search for more accurate variables of neonatal risk. This study aimed at identifying potential prognostic factors for neonatal mortality among newborns referred to intensive care units.

METHODS

A birth cohort study was carried out in the municipality of Goiânia, Central Brazil. Goiânia has a population of 1,093,007 inhabitants, 20,286 live births per year and infant mortality estimated at 15.5 deaths per 1,000 live births.[13] Study inclusion criteria included newborns living in Goiânia who have been admitted in any of the nine NICU during the neonatal period (zero to 28 days of age) from November 1999 to October 2000. NICU characteristics are presented in Table 1.

Information on all registered live births and deaths

Table 1 - Characteristics of neonatal intensive care units. Goiânia, Brazil, 2000.

Unit	Health Care Insurance	Type of health unit	Cots (N)
1	Public-funded universal health insurance and private	Pediatric hospital	10
2	Public-funded universal health insurance and private	General hospital	9
3	Private	Maternity hospital	4
4	Private	Maternity hospital	12
5	Public-funded universal health insurance and private	General hospital	8
6	Public-funded universal health insurance and private	Pediatric hospital	15
7	Public-funded universal health insurance and private	Pediatric hospital	8
8	Public-funded universal health insurance and private	Pediatric hospital	10
9	Public-funded universal health insurance	University hospital (pediatric, maternity)	9

in Brazil are routinely collected by local registrars and forwarded to the Brazilian Ministry of Health.[13] Linked birth and infant death certificates of Goiânia residents were used to ascertain the cohort of live born infants by using the national database, the SINASC and the SIM. As part of this study, an active surveillance system was established for neonatal intensive care mortality, in collaboration with the Department of Health (local), to minimize death underreporting. The investigation of neonatal deaths was carried out by the study team and government technicians. A database was created with information extracted from death certificates and completeness of certificate data was maximized through the surveillance system by reconciling records from hospitals, where neonates were born and then admitted, with mother's delivery care records. Ninety percent of all infant death records were successfully matched to their corresponding birth records; 10% could not be matched as newborns resided outside the municipality and therefore were excluded from the analysis. The final linked database had a total of 875 newborns, which comprised the study population. The outcome included 713 survivors and 162 NICU deaths in the neonatal period. Exposure variables and their corresponding categorization were extracted from birth and death certificates. For continuous variables, infant's birth weight and 5-min Apgar score, stratification was performed according to the World Health Organization (WHO) standards.[22]

The prognostic factors for neonatal death were analyzed in a Cox's proportional hazards model taking into account the time of death after admission in the NICU. Relative risks were calculated as proportional hazards ratios for each predictor variable in the univariate model. Variables with p-values less than 0.10 were assessed as independent predictors using the multivariate Cox's proportional hazards model with the likelihood ratio test statistic.[7] The proportional hazard assumption was graphically analyzed using the log (-log) survival curve (cumulative hazard).

Further analysis was conducted using the Receiver Operating Characteristic (ROC) curve[6] to compare the performance of statistically significant prognostic factors in the multivariate Cox's model, discriminating between neonatal death and survival. The ROC curve was constructed by plotting sensitivity (correct prediction of death) against 1 – specificity (correct prediction of survival) on the y and x axes, respectively, and by calculating the area under the curve (Az). The area under the curve was used to represent prediction precision. Differences between variable's Azs were evaluated through a comparison of the 95% CI of the corresponding areas. Az's confidence intervals that excluded 0.5 were considered significant results. An expected mortality rate was calculated from the average of the predicted death probability for each NICU. Hospital specific ratios of observed to expected mortality rates were then multiplied by the overall mortality rate for the study period to obtain the risk mortality rate adjusted for Apgar score and birth weight, which was then plotted with 95% confidence intervals.[9] Analyses were carried out using Epi Info 6.04d and SPSS statistical package (version 10.0.1). All reported p-values were two-sided and values below 0.05 were considered significant.

RESULTS

During the 12-month study period, 20,286 live births were recorded in the municipality. A total of 216 newborns died during the neonatal period, of which 162 (75%) were in the NICU. Fifty-four out of 216 newborns who died before reaching the NICU were not included in the study. The overall probability of neonatal death in Goiânia was 10.6/1,000 while mortality rate for newborns admitted to the NICU was 18.6% (95% CI: 16.0-21.4). There was a wide range in the crude mortality rate from 9.5% to 48.1% among the nine NICU (Figure 1). After adjusting for birth weight (<2,500 g *vs*. ≥2,500 g) and Apgar score (<7 *vs*. ≥7), NICU numbers 8 and 9 had mortality rates significantly higher than the mean for the nine NICU, whereas sites number 1 and 4 had lower adjusted mortality rates (p<0.05).

Of 162 deaths, 31 occurred in the first twenty-four hours after NICU admission; most of these newborns weighted less than 2,500 g. Those aged less than 20 years were mothers of 23.5% newborns admitted to NICU and 47.8% of them had only completed elementary school. The majority (83.0%) of

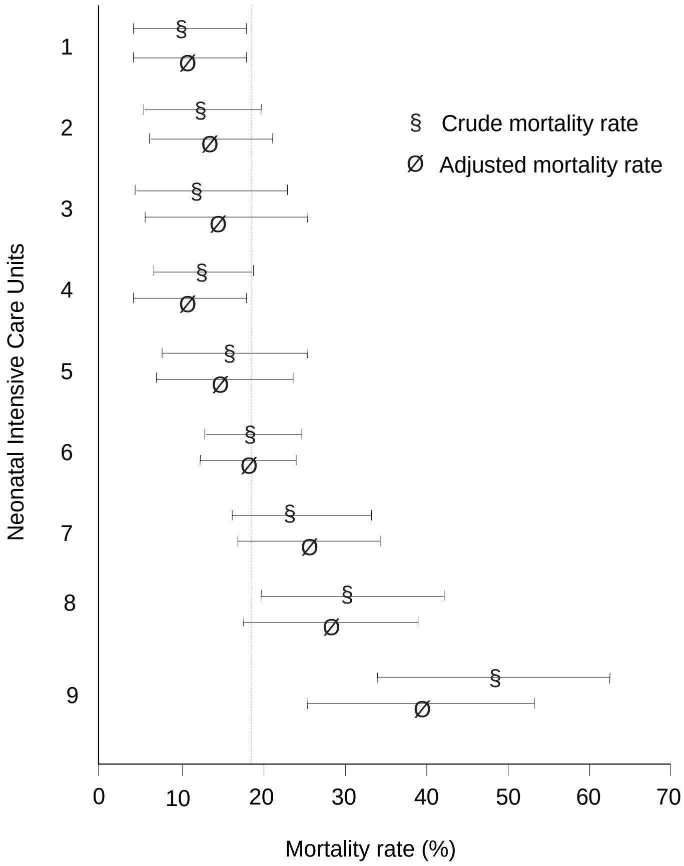

Figure 1 - Crude and adjusted mortality rates (by birth weight and 5-min Apgar score) for neonates admitted to nine neonatal intensive care units (identified by numbers). Horizontal bars denote 95% confidence intervals. Dashed lines indicate the mean for the nine hospitals.

low birth weight infants were preterm. The public health system covered 73.1% of the admissions. Among those admitted to NICU 62% were delivered through cesarean section and 12.8% died within the first 24 hours. Significant predictors of neonatal death in the univariate analysis were as follows: public coverage, single pregnancy, less than four prenatal visits, vaginal delivery, low birth weight, gestational age less than 37 weeks and 5-min Apgar score less than seven (Table 2). To control for potential confounding effect of both birth weight and type of delivery, a stratified analysis was performed. Cesarean section was associated with lower neonatal mortality rate only for newborns with less than 2,500 g ($p<0.05$). While a statistically significant interaction was found between birth weight and type of delivery ($\chi^2=11.86$, $p<0.001$), no interaction was observed between gestational age and Apgar score (p=0.76). Single pregnancy, low birth weight, and Apgar score less than seven remained independently associated to death in the multivariate Cox proportional hazards model analysis. Infants weighing less than 1,500 g had a 2.93 (95% CI: 1.39-6.15) risk of dying when compared to the newborns weighing ≥2,500 g.

Figure 2 compares the areas under the ROC curves for those variables independently associated with neonatal death in the multivariable Cox regression model. Birth weight and Apgar score were entered as continuous variables. Both areas below the ROC curves were significantly greater than 0.5. However, no significant statistical difference was found when comparing the areas under the ROC curve for birth weight (Az=0.71; 95% CI: 0.65-0.77) and 5-min Apgar score (Az=0.71; 95% CI: 0.67-0.76). Table 3 shows the sensitivity and specificity obtained for different values of birth weight using the results generated by the ROC curve. Thus, birth weight equal to 2,500 g as a cutoff value had 72.2% sensitivity (95% CI: 64.6-79.0) and 54.0% specificity (95% CI: 50.2-57.8) for the selection of infants at risk of dying.

DISCUSSION

The strength of this study relies on the fact that it included infants of all birth weights and all NICU serving a metropolitan region. The

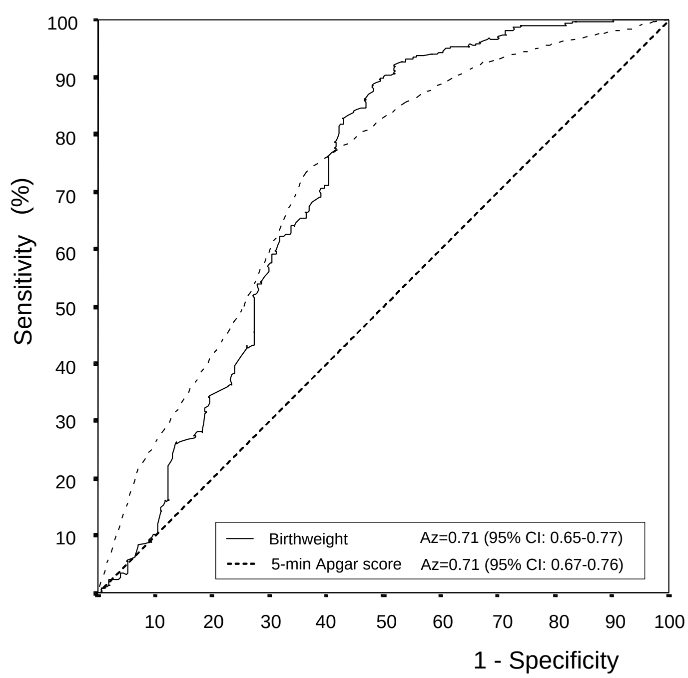

Figure 2 - Receiver operating chacacteristic (ROC) curves of the performance of birth weight and 5-min Apgar score in predicting mortality in neonatal intensive care units.

mean birth weight of newborns admitted to the NICU was 2,445 g (95% CI: 2,388-2,502) and 20.9% of them had Apgar score lower than seven, while in the neonatal cohort as a whole the corresponding values were 3,208 g (95% CI: 3,200-3,215) and 1.7%, respectively.

Birth weight and 5-min Apgar score were found to be independent predictors of neonatal mortality and had similar accuracy in discriminating the groups of newborns at high risk for death. While Apgar score can be somewhat inaccurate due to subjective evaluation, birth weight provides a more precise measurement for screening neonates at risk of dying. The cutoff value of 2,500 g for birth weight achieved the best performance for predicting neonatal death with sensitivity higher than 70%. Birth weight has been widely recognized as a powerful predictor of infant death, alone or in conjunction with other potential risk variables.[10,21] In NICU of developed areas, including some settings in Brazil, birth weight has been mostly used as part of complex scoring systems, such as CRIB and SNAP, to assess illness severity.[23] In the study setting, the lack of well-developed and implemented healthcare insurance has impaired the access to these laboratory testing. The methodological rationale adopted in this study allowed for identifying birth weight as a prognostic risk variable of neonatal death, and also as a screening variable for neonatal death for public health purposes. The 0.71 accuracy of birth weight in predicting mortality for neonates admitted to NICU was slightly lower than that reported in Brazil.[23]

Results of several studies conducted in developing and developed regions have found gestational age as a

Table 2 - Hazard ratios for neonatal mortality according to prognostic factors. Goiânia, Brazil, 1999-2000.

Prognostic variables	Deaths[a] (N)	Hazard Ratio[b] (95% CI)	
		Univariate	Multivariate
Socio-economic			
Mother's schooling (years)			
≥12	195 (32)	1.0	
8-11	279 (56)	0.92 (0.57-1.47)	
4-7	252 (53)	1.05 (0.66-1.68)	
0-3	65 (14)	1.19 (0.59-2.38)	
Type of health insurance			
Private	213 (29)	1.0	1.0
Public health system	580 (132)	1.57 (0.99-2.49)*	1.42 (0.80-2.53)
Marital status			
Married	572 (106)	1.0	
Not married	265 (54)	1.11 (0.77-1.62)	
Maternal			
Mother's age (years)			
<20	203 (37)	1.0	
20-34	593 (108)	1.07 (0.70-1.64)	
>34	67 (16)	1.61 (0.87-2.97)	
Multifetal pregnancy			
Yes	112 (16)	1.0	1.0
No	758 (146)	1.78 (0.98-3.22)*	1.98 (1.05-3.69)**
Prenatal visits			
≥7	537 (84)	1.0	1.0
4-6	205 (40)	1.10 (0.72-1.70)	0.75 (0.47-1.23)
1-3	60 (22)	2.05 (1.21-3.46)***	0.75 (0.30-1.22)
None	10 (6)	5.34 (2.31-12.30)***	1.26 (0.63-4.50)
Gestational age (weeks)			
≥37	410 (43)	1.0	1.0
<37	415 (107)	2.32 (1.54-3.49)****	1.40 (0.73-2.70)
Siblings alive			
None	477 (85)	1.0	
1	260 (49)	0.98 (0.65-1.47)	
2	107 (24)	1.59 (0.99-2.56)	
≥3	31 (4)	0.64 (0.20-2.04)	
Type of delivery			
Cesarean section	539 (69)	1.0	1.0
Vaginal	330 (92)	2.04 (1.45-2.89)***	1.32 (0.85-2.05)
Child			
Sex			
Female	350 (57)	1.0	
Male	525 (105)	1.28 (0.89-1.83)	
Birth weight (g)			
≥2,500	430 (47)	1.0	1.0
1,500-2,499	293 (39)	1.09 (0.70-1.77)	1.09 (0.57-2.13)
1,000-1,499	90 (45)	4.02 (2.53-6.40)****	2.93 (1.39-6.15)****
<1,000	38 (31)	9.18 (5.33-15.80)****	5.87 (2.40-14.33)****
5-min Apgar score			
7-10	672 (83)	1.0	1.0
4-6	141 (52)	2.76 (1.87-4.06)****	1.80 (1.00-2.45)***
0-3	37 (19)	3.78 (2.09-6.83)****	2.25 (1.29-5.34)**

[a]Missing values for any predictor were excluded from the analysis, so the total does not always equal to 875.
[b]Cox's proportional hazards model
CI, Confidence Interval *p<0.10; **p<0.05; ***p<0.01; ****p<0.001

Table 3 - Combination of different sensitivity and specificity to define the cut-off value of birth weight for the screening of high-risk newborns.

Birth weight (g)	Sensitivity (95% CI)	Specificity (95% CI)
2,500	72.2 % (64.6-79.0)	54.0% (50.2-57.8)
2,000	61.1% (53.1-68.7)	75.0% (71.6-78.2)
1,500	48.1% (40.2-56.1)	92.0% (89.7-93.9)
1,000	21.6% (15.8-28.4)	99.0% (97.9-99.6)

powerful predictor of neonatal mortality.[2,18] The univariate analysis of that study showed that preterm newborns had 2.32 risk of dying compared to term newborns. However, multivariable analyses showed this relationship was not significant regardless of birth weight and 5-min Apgar scores. That is, after controlling for birth weight and Apgar scores, gestational age did not predict neonatal death. A likely explanation to these findings could be the close relationship between gestational age and Apgar scores, as preterm infants are frequently related to low 5-min Apgar.[3,17] Higher mortality rates have been shown among preterm infants with fetal growth restriction compared to those appropriate-for-gestational-age infants.[12] Similarly to the present study some investigators observed that preterm twins (<37 weeks) had lower neonatal mortality than singletons of the same gestational age, probably because twins reach an earlier fetal pulmonary maturation and also have a faster placental development.[5,11,16] Since gestational age is recorded as a categorical variable in the SINASC instead of being recorded as complete weeks, the measurement of birth weight percentiles in relation to gestational age was not feasible.

Some limitations of the present study should be addressed. Data were restricted to infants admitted to NICU and hence did not cover deaths of those who did not reach any specialized care. Combining data on NICU deaths with data on deaths occurring in other settings should yield information on predictors of neonatal deaths for all infants born in the municipality, which may be helpful for those counseling pregnant women. In this sense, further studies should assess suitable algorithms useful for screening all neonates and infants. Moreover, as only those variables found in the Brazilian data systems were assessed, there was a lack of refined clinical information on disease severity, a potential confounder. These data are not recorded on a standardized basis in NICU thus they could not be used as a source of data. Therefore, clinical information on pregnancy and delivery is out of the scope of this study. The interpretation of results derived from secondary data requires some thought. SIM and SINASC have been established in 1975 and 1990, respectively. At present, Goiânia local birth record system covers 99% of the estimated number of live births by the Brazilian Census Bureau.[13] Underreporting of infant deaths by the death record system, currently estimated as 15%, was minimized by the ongoing active surveillance of death. Even though, there were some difficulties posed by missing data. Despite these issues, linkage of infant's death certificates to their corresponding birth certificates has been increasingly used as a methodological strategy for building-up systems for tracking infant mortality.[1,15]

In Goiânia nearly 70% of deaths before the first year of life occur during the neonatal period.[15] The present study consists of a population-based birth cohort since it comprises all live newborns, all neonatal deaths of Goiânia residents, and also all NICU. Moreover, the birth cohort admitted to the NICU covers about 75% of deaths occurred in these units, where care is delivered to all newborns at risk in the municipality. The reliability of SINASC data has been well documented for birth weight and Apgar score in recent studies.[14,20] In fact, 88% agreement was seen between maternity records and SINASC data for birth weight and Apgar score (data not shown). In the year of 2000 in Goiânia, data on birth weight and 5-min Apgar score were missing in the SINASC only in 0.4% and 1.1% of the records, respectively.

A relative high proportion (49.1%) of newborns with birth weight above 2,500 g was admitted to NICU in Goiânia, corroborating the results found in studies carried out in NICU in Canada (47.7%).[18] The study results suggest that newborns were referred to NICU following different criteria, as a high number of infants were admitted with Apgar above seven. This can probably be explained because Goiânia has no neonate intermediate care units. Variations in risk-adjusted rates of deaths across NICU have been described in the literature. A considerable variation of mortality rates across neonatal intensive care units was found. However, the overall mortality rate was higher than that reported in São Paulo (5.9%) and in developed areas, like Canada (4%), even considering published data for very low birth weight mortality.[18,24] Some characteristics of the neonatal care in Goiânia, such as low use of surfactant, inadequate technology, small neonatal units (all of them ≤15 cots), and non-availability of specialists could contribute to the high neonatal mortality detected in Goiânia NICU. Two sites presented significant high mortality rates, regardless of birth weight and 5-min Apgar score. These two units with the highest mortality rates admit from low-income infants. One of them is a university hospital, which serves exclusively the public health sector and is a reference center for high-risk pregnancies in the state. The differences in adjusted mortality rates detected herein could be used to target local units that should be further investigated for in-depth assessment of quality of neonatal care.

There are ongoing studies to examine practice differences among the study NICU to gain insight as to ways of reducing deaths in these specific units. The results of the present study suggest that surveillance programs for neonatal death should include preventive actions and interventions for the delivery period. Focused initiatives for quality improvement may also be necessary in specific institutions, prioritizing those NICU with higher mortality rates. Development of strategies aimed at addressing these issues is key to further reducing NICU deaths.

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