

The use of Cox regression to estimate the risk factors of neonatal death in a private NICU

Uso da regressão de Cox para estimar fatores associados a óbito neonatal em UTI privada

Uso de la regresión de Cox para estimar factores asociados a óbito neonatal en UTI privada

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ABSTRACT

Objective: To estimate the risk factors associated with neonatal deaths in a Neonatal Intensive Care Unit of a private hospital in the city of Taubaté (SP), Brazil, from 2005 to 2007, using the Cox regression analysis.

Methods: Longitudinal epidemiological study with data retrieved from medical records of all newborn admitted to a private Neonatal Intensive Care Unit from January 2005 to December 2007. The primary outcome was the neonatal mortality and independent variables were those concerning maternal and neonatal characteristics. Univariate analysis included chi-square test, relative risk and the Kaplan-Meier survival plot for each variable. Multivariate analysis to test association of independent variables with neonatal mortality was performed by Cox regression analysis.

Results: 185 neonates were enrolled in the study and 10.5% died before the 28th day of life. Variables that were significantly associated to neonatal death by the Cox regression analysis model were birthweight <1500g, 5th minute Apgar score <7, mechanical ventilation and previous stillbirth.

Conclusions: The variables with good adjustment in the Cox model for neonatal death are those associated to pre-natal maternal care and the quality of infant's care in the Neonatal Intensive Care Unit.

Key-words: neonatal mortality (Public Health); survival analysis; intensive care, neonatal.

RESUMO

Objetivo: Estimar os fatores de risco associados ao óbito até 28 dias após o nascimento de recém-nascidos internados entre os anos de 2005 a 2007 em uma Unidade de Terapia Intensiva Neonatal de hospital privado no Município de Taubaté, usando a análise de regressão de Cox.

Métodos: Estudo epidemiológico do tipo longitudinal. Os dados foram obtidos de prontuários de todos os recém-nascidos internados na Unidade de Terapia Intensiva Neonatal, no período de janeiro de 2005 a dezembro de 2007. Foram obtidas variáveis maternas e relativas ao recém-nascido, sendo o desfecho primário a mortalidade neonatal. Foi feita a análise univariada, utilizando teste do qui-quadrado, risco relativo e gráfico de Kaplan-Meier para cada variável separadamente. A análise multivariada foi realizada por meio da regressão de Cox para verificar a associação de fatores maternos e neonatais ao desfecho primário.

Resultados: Foram estudados 185 neonatos, dos quais 10,5% foram a óbito antes do 28º dia de vida. As variáveis que se associaram de modo significativo ao óbito no modelo de Cox foram: peso <1500g, Apgar no 5º minuto <7, ventilação mecânica e óbito fetal anterior.

Conclusões: As variáveis com bom ajuste no modelo de Cox relacionadas ao óbito neonatal refletem a assistência prestada à mãe no período pré-natal e o cuidado oferecido ao recém-nascido na Unidade de Terapia Intensiva.

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Palavras-chave: mortalidade neonatal; análise de sobrevivência; terapia intensiva neonatal.

RESUMEN

Objetivo: Estimar los factores de riesgo asociados al óbito hasta 28 días después del nacimiento de recién-nacidos internados entre los años de 2005 y 2007 en una Unidad de Terapia Intensiva de un hospital privado en el Municipio de Taubaté (São Paulo, Brasil), usando el análisis de regresión de Cox.

Métodos: Estudio epidemiológico de tipo longitudinal. Los datos fueron obtenidos de prontuarios de todos los recién-nacidos internados en las UTI neonatal privadas en el periodo de enero/2005 a diciembre/2007. Se obtuvieron variables tanto maternas como relativas al recién-nacido y categorizadas, siendo el desfecho primario la mortalidad neonatal. Se realizó el análisis univariado utilizando la prueba de chi cuadrado, el riesgo relativo y la gráfica de Kaplan-Meier para cada variable en separado. El análisis multivariado fue realizado por medio de la regresión de Cox para verificar la asociación de factores maternos y neonatales al desfecho primario.

Resultados: Entraron en el estudio 185 neonatos, siendo que 10,5% fueron a óbito antes del 28º día de vida. Las variables que se asociaron de modo significativo al óbito en el Modelo de Cox fueron: peso <1.500g, Apgar 5 minutos <7, ventilación mecánica y óbito fetal anterior.

Conclusiones: Las variables con buen ajuste en el Modelo de Cox asociadas al óbito neonatal reflejan la asociación del óbito neonatal a la asistencia prestada a la madre en el periodo prenatal y también al cuidado ofrecido al recién-nacido en una unidad de terapia intensiva.

Palabras clave: mortalidad neonatal; análisis de sobrevivencia; terapia intensiva neonatal.

Introduction

Infant mortality rates are a major indicator of the quality of life of a population. The concept of infant mortality can be broken down into two components: neonatal and postneonatal mortality⁽¹⁾. Neonatal mortality includes all deaths occurring before the 28th day of life, whereas postneonatal mortality encompasses all deaths occurring between the 28th day of life and the day before the child's first birthday⁽²⁾. Neonatal mortality can be further subdivided into early (occurring before the seventh day of life) or late neonatal mortality (occurring thereafter). This subdivision

is necessary, because the causes of early and late neonatal mortality are distinct.

The extent to which the neonatal component contributes to overall infant mortality is proportional to the development status of each country, as improved social and environmental conditions lead to reductions in postneonatal mortality⁽¹⁾. Nevertheless, even in developing countries, where risk factors for postneonatal mortality are still quite significant, the neonatal component accounts for more than half of the overall infant mortality rate⁽³⁾. In Brazil, infant mortality rates have been declining, mostly due to reductions in postneonatal mortality in the North and Northeast regions of the country. In the South and Southeast regions of Brazil, neonatal mortality is declining as well⁽⁴⁾. In 2001, the overall neonatal mortality rate was 12.92 deaths/1000 live births for the country as a whole and 11.89 deaths/1000 live births in Southeast Brazil; by 2007, rates had declined to 10.66/1000 for the country as a whole and 9.44/1000 in the Southeast region⁽⁵⁾.

There is broad consensus in the literature that neonatal mortality is due to a close, complex relationship between biological, socioeconomic, and care-related variables^(2,4,6). Identifying and understanding these factors—which include low and very low birth weight, preterm or very preterm birth, adequate prenatal care, and adequate care during delivery and labor—can lead to a reduction in neonatal mortality rates. Studies meant to assess the influence of these variables on neonatal mortality may have descriptive designs⁽⁷⁾, be based on logistic regression techniques^(8,9), or even take a spatial analysis approach, with use of geoprocessing methods⁽¹⁰⁾.

In studies that employ survival analysis, “survival time” is defined as the time elapsed between study entry and occurrence of the outcome of interest (usually death or disease, known as “failure”) or loss to observation (known as “censoring”)⁽¹¹⁾. The Cox proportional hazards model is a multiple regression analysis method employed in survival analysis. It is particularly indicated when the objective is to estimate the role of independent variables that act as risk multipliers⁽¹¹⁾.

In this context, the present study sought to estimate the risk factors associated with neonatal death among infants admitted to a private neonatal intensive care unit (NICU) in the municipality of Taubaté, state of São Paulo, Brazil, between 2005 and 2007, by means of Cox regression analysis.

Method

This longitudinal epidemiological study employed survival analysis methods and Cox multiple regression

modeling. In epidemiological studies, the variable of interest is always the dependent variable. In some settings, this will be the time until a certain endpoint, such as disease or death, is reached. Cox models enable identification of which independent variables act as intensifiers, when analyzed as a set, and takes into account their statistical significance within a confidence interval.

Data were obtained from the medical records of all neonates admitted to a private NICU between 1 January 2005 and 31 December 2007. Only those infants who died before the 28th day of life were considered. Patients whose charts were missing relevant data were excluded from the sample. The NICU in which the study was conducted is a six-bed unit that accepts both intramural transfers and referrals from other municipalities in the Taubaté region. It cares exclusively for high-risk neonates, defined as those with low or very low birth weight, prematurity, illness requiring hospitalization, congenital malformations, of 5-minute Apgar scores <7.

Variables were categorized into one of two classes to enable multivariate regression analysis. Neonatal variables were categorized as follows: *birth weight*, very low (<1500g), low (1500-2499g), or normal (\geq 2500g); *gestational age*, preterm (<37 weeks) or full-term (\geq 37 and <42 weeks); *Apgar scores at 1 and 5 minutes*, high-risk (\leq 6) or adequate (\geq 7); *weight-for-age adequacy*, high-risk (small for gestational age [SGA]) or large for gestational age [LGA]) or adequate, according to the Battaglia and Lubchenco intrauterine growth curves⁽¹²⁾; *venous access*, high-risk (umbilical) or adequate (PICC or none); and presence or absence of *malformations*. Maternal variables were defined as: *age*, high-risk (<20 and >34 years) or adequate (20-34 years); and *number of live offspring*, high-risk (none or more than two) or adequate (one or two). The following clinical conditions were analyzed and defined as present, if diagnosed by the unit neonatologist and noted in the patient's chart, or absent: infant respiratory distress syndrome, bronchopulmonary dysplasia and sepsis (confirmed clinically or by blood cultures), mechanical ventilation through endotracheal tube, orotracheal intubation, and parenteral nutrition (PN).

Univariate analysis was performed in the Stata 9 software environment for identification of which variables were associated with neonatal death, by means of chi-square testing, calculation of relative risk, and Kaplan-Meier curves of each variable. The results of univariate analysis allowed determination of the relative risk of neonatal death with a 95% confidence interval for each variable. Tables were

constructed with mean birth weight, duration of pregnancy, one- and five-minute Apgar scores, and length of stay values, stratified by outcome (discharge or death), using the Student *t* statistic, the relative risk (RR) values of all variables with $p < 0.20$, and the variables included in the final model.

Multivariate analysis included only those variables with a *p*-value of 0.20 or lower on univariate analysis. After this step, all variables with $p < 0.20$ were analyzed as a set. The final model included all variables with $p < 0.05$. Multivariate analysis was used to calculate hazard ratios, that is, the odds of death divided by the odds of survival⁽¹¹⁾. Finally, martingale residuals were plotted to estimate the goodness of fit of the model.

The present study was approved by the Universidade de Taubaté Research Ethics Committee.

Results

During the three-year study period, 198 infants were admitted to the NICU. Of these 198, 13 were excluded from statistical analysis due to a lack of relevant information in their medical records or when lost to follow-up due to transfer out of the NICU. The final sample thus comprised 185 neonates, 19 of whom (10.3%) died before the 28th day of life.

Ninety-five mothers (71.4%) were aged 20–34, and 52 patient records lacked information on maternal age. One hundred and ten mothers (79.1%) had one or two children; 46 patient records had no information on number of living children. Five mothers (4.9%) had a history of fetal death. Thirty-nine mothers (21.1%) were hypertensive, and 124 (67.0%) had no premature rupture of membranes. Only 11 (5.9%) mothers reported antenatal corticosteroid use. Cesarean section was the mode of delivery in 154 (86.3%) pregnancies.

Mean patient weight was 2163 \pm 797g, and mean gestational age, 34.0 \pm 3.4 weeks. The majority of infants were female (51.9%), with a birth weight of >1500g (80.0%), premature (79.6%), adequate for gestational age (83.3%), the product of singleton pregnancies (88.6%) and had 1- and 5-minute Apgar scores \geq 7 (78.1 and 91.5% respectively).

Concerning resuscitation in the delivery suite, 27% of neonates received oxygen, 19.4% required bag-valve-mask ventilation, 3.25% were intubated, 2.7% required chest compressions and 1% received drugs. Most patients had a body temperature of <37.5°C on admission. In terms of IV access, 117 neonates (63.2%) had a PICC or umbilical

catheter at the time of NICU admission. Parenteral nutrition was administered to 127 patients (68.7%). One hundred and four neonates (56.8%) did not require CPAP, 59 did not undergo phototherapy (36.9%) and 83 (44.9%) did not require mechanical ventilation; likewise, 105 (56.8%) did not require an oxygen hood and 160 (79.3%) did not require $\text{FiO}_2 > 50\%$.

Regarding morbidity, 32 neonates (17.4%) were diagnosed with hyaline membrane disease, 62 (33.6%) with neonatal sepsis, 14 (7.5%) with bronchopulmonary dysplasia and 15 (8.1%) with congenital malformations.

Neonatal characteristics, stratified by outcome (alive vs. deceased after 28 days) are shown in Table 1. Statistically significant between-group differences were found for all variables. Univariate analysis for the outcome of neonatal death, including those variables with $p < 0.20$, is described in Table 2.

Kaplan-Meier survival analysis was performed on this new set of variables. Those variables whose Kaplan-Meier curves did not cross at the halfway point of the study period (weight $< 1500\text{g}$, SGA or LGA, 1- and 5-minute Apgar < 7 , intubation, chest compressions, mechanical ventilation, history of fetal death, and antenatal corticosteroid use) were kept. After adjustment of multivariate analysis, the variables weight $< 1500\text{g}$, 5-minute Apgar scores < 7 , mechanical ventilation, and history of fetal death were carried over to the model. Adjusted HRs and p-values for these variables are shown in Table 3.

Very low birth weight neonates accounted for only 20% of all admissions, versus 73.6% of all deaths. According to multivariate analysis, the odds of death in this group were nearly 11 times greater than those of normal birth weight infants. Five-minute Apgar scores were below 7 in only 8.5% of all neonates, but occurred in 29.4% of those who died; patients with low scores had fivefold odds of neonatal death. Overall, 43.7% of neonates required mechanical ventilation, versus 68.4% of those who did not survive to 28 days; neonates requiring mechanical ventilation had nearly threefold odds of death when compared to those who did not require ventilator support. Prior fetal deaths were reported by 4.4% of all mothers in the sample and 26.3% of mothers whose infants died in the neonatal period; the odds of neonatal death were six times greater among infants whose mothers had a history of fetal death. All variable included in the final model were analyzed by the Cox-Snell residuals method (Figure 1). This approach measures the differences between expected or model-estimated values and actually

observed values; the lesser the difference, the more the expected values curve approaches the optimal curve (dashed diagonal line in Figure 1).

Table 1 - Mean values for the variables gestational age, birth weight, 1- and 5-minute Apgar scores and length of NICU stay, Taubaté, 2005–2007.

	Discharge	Death	p-value
Gestational age (weeks)	34.6	29.7	< 0.01
Birth weight (g)	2256	1405	< 0.01
1-min Apgar	7.2	4.3	< 0.01
5-min Apgar	8.6	6.8	< 0.01
Length of stay (days)	19.6	7.0	< 0.01

Table 2 – Univariate analysis with relative risks (HR) and 95% confidence intervals (95%CI) for neonatal death in a private NICU, Taubaté, São Paulo, 2005–2007.

	HR	95%CI	p-value
Weight $< 1500\text{g}$	12.04	4.32-33.54	< 0.001
Male gender	0.45	0.17-1.20	0.10
1-min Apgar < 7	2.66	1.01-6.99	0.04
5-min Apgar < 7	5.25	1.84-14.96	0.002
Endotracheal intubation in delivery suite	5.62	1.62-19.40	0.006
Chest compressions in delivery suite	7.77	2.25-26.80	0.001
Resuscitation drugs in delivery suite	4.46	0.59-33.65	0.147
SGA or LGA [#]	2.28	0.86-6.03	0.094
Mechanical ventilation	2.86	1.08-7.53	0.033
Oxygen hood	0.51	0.20-1.27	0.152
Phototherapy	0.21	0.04-0.92	0.039
Maternal age < 20 or > 34 years	0.21	0.02-1.69	0.145
Prior history of stillbirth	9.34	3.35-26.02	< 0.001
Hypertension	2.25	0.88-5.73	0.087
Antenatal corticosteroids	2.96	0.86-10.16	0.085

SGA: small for gestational age; LGA: large for gestational age.

Table 3 – Multivariate Cox regression model with relative risks (HR) and 95% confidence intervals (95%CI) for neonatal death in a private NICU, Taubaté, São Paulo, 2005–2007.

	Adjusted HR	95%CI	p-value
Weight $< 1500\text{g}$	10.98	3.57-33.17	< 0.001
5-min Apgar < 7	5.25	1.57-17.46	0.007
Mechanical ventilation	2.90	0.99-8.45	0.051
History of fetal demise	6.46	1.96-21.26	0.002

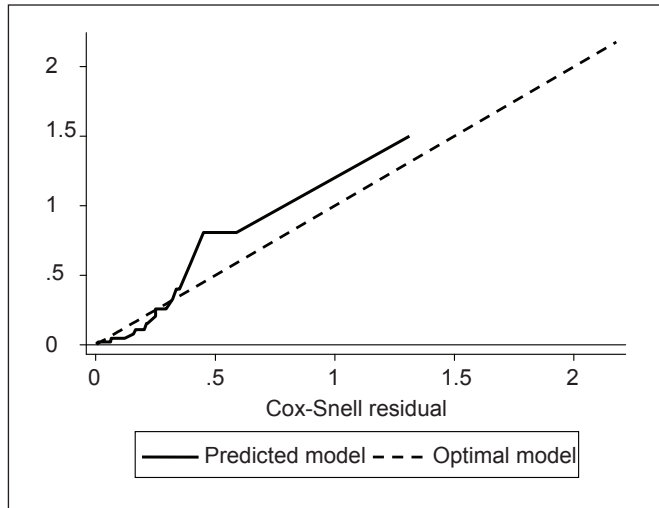


Figure 1 - Plot of Cox–Snell residuals for neonatal death in a NICU in Taubaté, São Paulo, 2005–2007.

Discussion

With the exception of one study on NICU mortality carried out in Goiânia, state of Goiás⁽¹³⁾, which employed the Cox proportional hazards model, all three other studies on neonatal death in the recent Brazilian literature employed logistic regression^(14–17) and focused on very low birth weight or preterm infants. Neonatal mortality studies can contribute substantially to assessments of quality of life in a given population. In the present study, risk factors associated with neonatal death were mostly related to biological, rather than quality of care-related, variables.

Suboptimal maternal age (older than 34 or younger than 20 years) was not considered a risk factor, which is consistent with the findings of previous studies carried out in Blumenau, Santa Catarina⁽⁹⁾, and Montes Claros, Minas Gerais⁽⁸⁾. Nevertheless, this finding disagrees with the conclusions of other studies that have reported decreased survival rates among infants born to adolescent mothers, which would be explained not only by the biological risks of maternal age, but also by other health-related dimensions, such as the stress of unplanned and sometimes unwanted pregnancies and the challenges of acceptance by the mother's family^(4,14). Our results may be explained by the study setting: a private hospital, which most likely treats patients with a higher socioeconomic status and greater educational achievement—that is, a population from which greater attention to family planning is expected.

Although variables concerning maternal educational achievement and number of prenatal visits (both of which

reflect socioeconomic level) were not considered in the present study, one may speculate that these variables would not be associated with neonatal mortality in the sample, as the characteristics of the study population are consistent with improved access to health care and greater awareness of the importance of prenatal care. Countless studies have reported associations between low educational achievement and neonatal death^(7,9), which suggests that access to formal schooling leads to improved awareness of health education⁽⁴⁾. According to Almeida and Barros⁽⁶⁾, the number of prenatal visits is no assurance of the quality of prenatal care, particularly in regions with ample prenatal care coverage. Schoeps *et al.*⁽⁴⁾, analyzed the quality of prenatal care and found it to be far more important than the number of visits.

Infant gender was not associated with neonatal death in our sample; this is consistent with some prior studies^(6,8,18) and disagrees with others, which have found male gender to be a risk factor. In a cohort study of over 4000 preterm neonates, Tyson *et al.*⁽¹⁹⁾ found that male gender was associated with increased risk of death on multivariate analysis. Although the mechanisms behind these findings are still unclear, some authors have suggested that male infants are subject to a higher incidence of lung immaturity and respiratory syndromes^(3,16,17), which are a leading cause of neonatal death.

As in the study carried out in Montes Claros, state of Minas Gerais, mode of delivery was not associated with risk of neonatal mortality in our sample; 86.7% of NICU patients and 88.8% of non-surviving neonates were delivered by Cesarean section⁽⁸⁾. Cesarean birth may have a protective effect against neonatal death, particularly when performed in private facilities, which treat mothers whose biological conditions and healthcare profile are conducive to neonatal survival. The true role of this variable is debatable, but our finding is consistent with those of several prior studies^(3,8–10).

Multiple pregnancy is associated with intrauterine growth restriction and preterm birth, and may consequently be associated with decreased neonatal survival rates. Indeed, a study conducted in Campinas, São Paulo, reported an association between twin pregnancy and increased mortality⁽⁶⁾. In the present study, 10.5% of neonates who died were the product of multiple pregnancies; this finding was not statistically significant, however. This is consistent with the results of previous research⁽³⁾, but stands in contrast to those of the large multicenter study carried out by Tyson *et al.*⁽¹⁹⁾. Our finding may have been due to the small number of multiple pregnancies in the study sample.

Intrauterine growth restriction (represented by SGA) and large size for gestational age (LGA) were significantly associated with death; on univariate analysis, SGA and LGA infants were twice as likely to die in the neonatal period as compared to adequate for gestational age (AGA) neonates. However, after inclusion in the Cox model, this variable became nonsignificant, possibly due to the stronger associations between low birth weight and low Apgar scores and death.

On univariate analysis, the only significant maternal variables were hypertension (26.3% of deaths) and antenatal corticosteroid use (15.7% of deaths). Conversely, in another study, antenatal corticosteroid use was found to be a major protective factor both on univariate and multivariate analysis; it plays an essential role in the management of preterm labor, as corticosteroids may speed lung development, thus reducing the odds of infant respiratory distress syndrome, which is often due to pulmonary immaturity⁽³⁾. In the present sample, few mothers received antenatal corticosteroids, and their use may have been associated with shorter duration of pregnancy, which indicates a significantly higher mortality rate in this subgroup of patients (extreme prematurity).

Half of all intubated infants died before the 28th day of life. This is consistent with the findings reported by Carvalho *et al*⁽⁵⁾. All variables related to resuscitation in the delivery suite were found to be significant on univariate analysis, which highlights the importance of preparedness for this type of intervention. In the present study, intubation was associated with a fivefold risk of death on univariate analysis, although it became statistically nonsignificant upon inclusion in the Cox model.

Mechanical ventilation has previously been reported as a major risk factor for neonatal mortality^(3,14). However, Carvalho *et al*⁽⁵⁾ note that this association may in fact be a confounder, as all neonates who died in their sample had received mechanical ventilation at some point. In the present study, mechanical ventilation, an intervention used in severe cases, was a statistically significant risk factor on univariate and multivariate analysis alike; the odds of death were three times higher in neonates requiring mechanical ventilation.

A history of fetal demise was reported by the mothers of 26.3% of infants who died in the neonatal period. In the Cox survival model, this factor was associated with a 7-fold risk of death, a finding similar to that reported by Almeida *et al*⁽⁶⁾ in a study conducted in the city of São Paulo. Negative outcomes of prior pregnancies, such as fetal death,

preterm birth, or low birth weight, may indicate that the mother has placental issues or other biological conditions that have an adverse effect on pregnancy and contribute to early neonatal death⁽⁴⁾.

One-minute Apgar scores <7 were associated with a two-fold risk of mortality on univariate analysis, although multivariate analysis showed no statistically significant effect; 5-minute Apgar scores <7 were associated with a fivefold increase in the odds of neonatal death. Both findings suggest that, the lower the infant's vitality at birth, the lower the odds of survival. This is consistent with the findings of several authors, and highlights the importance of the availability of supportive care measures for the management of neonates in this condition^(6,8).

In this study, prematurity did not meet statistical criteria for inclusion in univariate analysis, in stark contrast to the current scientific consensus, as preterm birth is considered a risk factor for neonatal death and is known to be associated with low birth weight^(1,8,9,19). One possible explanation for this finding is that both variables are highly correlated. Low birth weight is the single most important determining factor of neonatal mortality described in the literature^(1,4,6,8,9,18-20). In the present study, low birth weight was associated with 12-fold odds of mortality on univariate analysis, and remained a highly relevant factor after inclusion in the Cox survival model. According to Moraes Neto and Barros⁽²¹⁾, low birth weight infants are more vulnerable to metabolic derangements and lung maturity issues, which, when compounded by other morbidities, may lead to death. The authors also note that this variable and duration of pregnancy should not be analyzed in an isolated manner, but as influential mediators of other determinants of neonatal mortality. We may reasonably assume that, in the present study, the leading cause of low birth weight was prematurity, as we estimate that the mothers of all neonates in the sample had access to prenatal care. However, it bears stressing that our sample does not reflect the reality of the majority of the Brazilian population. This constitutes a major public health challenge; efforts must be made to increase the availability and quality of prenatal care and establish neonatal intensive care units to receive the products of high-risk pregnancies, as these infants may die if the medical technology they need is not available.

One limitation of the present study was the lack of information on relevant maternal conditions (such as socioeconomic status, educational achievement, and onset of prenatal care) and on patient origin (referred from within

the hospital or transferred from another facility). On the other hand, the study design enabled identification of a rarely researched variable, prior history of fetal demise, as a factor associated with neonatal death in the private NICU setting. The mortality rate found in this study (19 deaths, 10.5%) is consistent with that reported for Goiânia⁽¹⁴⁾, but diverges from the rates reported in a Brazilian multicenter

study of preterm infants with a birth weight of less than 1500g (5–31%)⁽¹⁵⁾ and is lower than those found by Carvalho *et al*⁽³⁾.

We conclude that, according to Cox survival analysis, low birth weight, low 5-minute Apgar scores, mechanical ventilation, and a history of fetal death are associated with neonatal mortality in a private NICU setting.

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