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# Risk factors for neonatal death in neonatal intensive care unit according to survival analysis

*Fatores de risco para óbito em unidade de terapia intensiva neonatal, utilizando a técnica de análise de sobrevida*

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## ABSTRACT

**Objective:** To identify risk factors associated with death in infants admitted to neonatal intensive care unit of Taubaté University Hospital.

**Methods:** This is a longitudinal study based on information from medical records regarding newborns admitted to the neonatal intensive care unit of Taubaté University Hospital. The outcome, either discharge or death, was the dependent variable. The independent variables were maternal and gestational variables: maternal age, hypertension, diabetes, corticosteroid therapy and delivery; the newborn variables: birth weight, gestation length, Apgar score in the first and fifth minutes of life, multiple birth, congenital malformations and gender; hospital variables: reports of mechanical ventilation, positive pressure ventilation, prolonged parenteral nutrition, sepsis, intubation, cardiac massage, phototherapy, hyaline membrane disease, oxygen and fraction of inspired oxygen. A model was built with three hierarchical levels for the survival analysis by the Cox model; the software Stata v9 was used, and the final model had variables with p value <0.05. The risks were estimated by the effect measure known as hazard ratio (HR) with 95% confidence intervals. Newborns transferred to other services during the hospitalization were excluded from the study.

**Results:** Were admitted during the study period 495 newborns, with 129 deaths (26.1%). In the final model, only the variables of corticosteroid use (HR 1.64, 95% CI 1.02-2.70), malformation (HR 1.93, 95% CI 1.05-2.88), very low birth weight (HR 4.28, 95% CI 2.79-6.57) and Apgar scores lower than seven by 1 min (HR 1.87, 95% CI 1.19-2.93) and 5 min (HR 1.74, 95% CI 1.05-2.88) and the variables phototherapy (HR 0.34; 95% CI 0.22-0.53) and intubation (HR 2.28, 95% CI 1 .41-3.70).

**Conclusion:** Factors related primarily to the newborn and the hospitalization (except corticosteroids therapy) were identified to be associated with mortality, highlighting a possible protective factor of phototherapy and the risk for very low birth weight infants.

**Keywords:** Infant mortality; Intensive care units, neonatal; Infant, low birth weight; Intensive care; Survival analysis; Infant, newborn; Congenital abnormalities

## INTRODUCTION

Survival analysis consists in determining study subjects' survival when exposed to the variables considered risk factor. It is currently known that the study of risk factors for infant mortality is very im-

portant, as, particularly in the newborn, it can be considered one of the best quality indicators for health care, as well as an indicator of population social and economic welfare.[1,2]

It is determined by multiple and complex factors related to biological, assistantial and social-economic variables, mainly in its neonatal component.[2-4]

Mosley & Chen[5] studies showed that this close and complex variables interaction may be better studied using hierarchical models, which allow the study of infant mortality determinants and their inter-relationships. Thus, distal factors (antecedents) influence intermediate factors, which in turn influence proximal factors (those acting more directly on the outcome). Thus, by means of a hierarchical structure, it is possible to consider and model distinct factors according to their time precedence and relevance for the outcome determination.[6]

With identification of risk factors, it is possible their prevention, particularly aiming the improvement of newborn children care.[1]

Here, neonatal intensive care units (NICUs) surge as hope, and one of the most effective tools to face this country's newborn mortality issue.[7] In this context, it can be said that the emergence of NICUs brought a widened universe for newborn assistance, offering improved survival for those who, few years ago, wouldn't be likely to survive.[8] It is important to highlight that it useless having a very complex assistance available if appropriate attention is not given to the prenatal and perinatal periods, and to the immediate newborn assistance in the delivery room.

NICU is an area set for treating newborns with a group of birth problems.

Thus, this study aims to identify the risk factors associated with death in newborns staying in the Taubaté University Hospital neonatal intensive care unit between in the years 2005 to 2007.

## METHODS

This is a longitudinal study, using the survival analysis technique. It was based on information extracted from the medical records of newborns staying in the neonatal intensive care unit of the Taubaté University Hospital (TUH).

The population consisted of born alive infants admitted between January 1st 2005 and December 31, 2007. Were considered cases the newborns with the outcome death, which in survival analysis is called "failure".

The dependent variable was the outcome, either discharge or death. The independent variables were maternal and gestational: maternal age, hypertension, diabetes, corticosteroid therapy and type of delivery; newborn variables: birth weight, pregnancy length, first and fifth minute Apgar score, multiple birth, congenital malformations and gender; hospitalization-related variables: reports of mechanic ventilation, positive pressure ventilation, long term parenteral nutrition, sepsis, intubation, cardiac massage, phototherapy, hyaline membrane disease, stay length (days) and inspired oxygen fraction.

A hierarchical model was built with three survival analysis levels in a Cox model; the Stata v9 software was used, and p value <0.05 variables remained in the final model. The risks were estimated by the hazard ratio (HR) with respective 95% confidence intervals. Were excluded from the study newborns transferred to other services during the hospital stay.

The maternal age variable was categorized as appropriate age (20 to 34 years old) or non-appropriate (others). Hypertension was categorized as present/absent, as well as were diabetes and prenatal corticosteroids use (administration time, dose and number of doses were not considered), and the delivery was categorized as either vaginal or surgical.

The newborns were categorized in three birth weight categories: very low birth weight (< 1,500 g), low birth weight (1,500 g to 2,499 g) and normal birth weight (≥ 2,500 g). Later, two categories were considered: very low birth weight (below 1,500 g) and others. Regarding the pregnancy length, the newborns were categorized as very preterm (up to 32 weeks of pregnancy), preterm (33 to 36 weeks + 6 days) and full term (37 weeks or more), later categorized in preterm (up to 36 weeks + 6 days) and full term. The fifth minute of life Apgar score was categorized in up to 6 (poor vitality) and 7 to 10 (good vitality). The first minute of life Apgar score was equally categorized. Multiple delivery was categorized as either present or absent.

Hospitalization-related variables: mechanic

ventilation, long term parenteral nutrition and sepsis (clinical and/or laboratory diagnosis) categorized as yes/no (present/absent). Inspired oxygen fraction was categorized as room air when no oxygen inspiration was installed other than room air (21%) and high for other values. Intubation, cardiac massage, phototherapy, hyaline membrane disease (clinical-radiological diagnosis) and oxygen therapy were also categorized as either present/absent (yes/no), and the hospital stay length was considered in days.

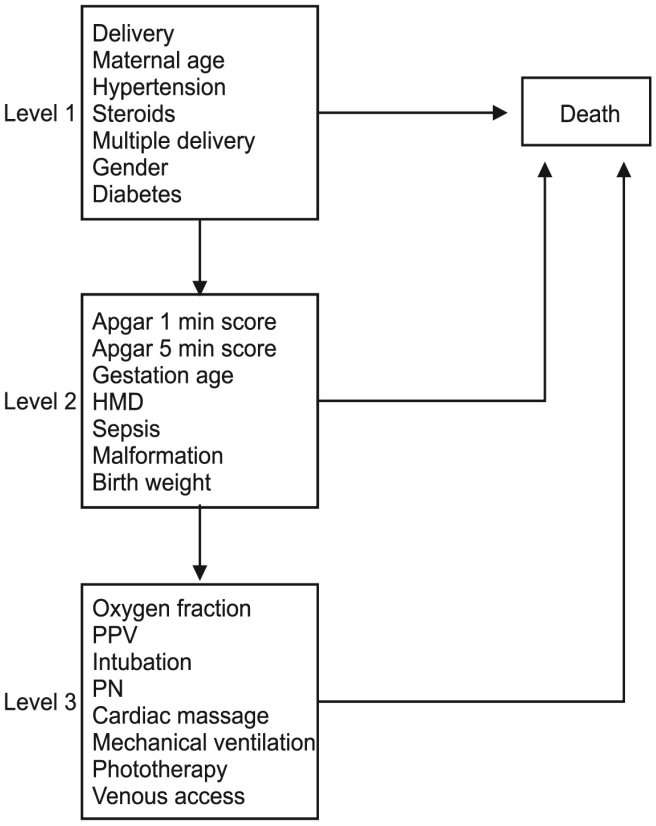
The data were bivariately analyzed to identify factors with p values <0.20. Next, these variables were evaluated together – multivariate analysis – by Cox regression. This approach provides the hazard ratio (HR), which dependent variable is failure as a function of hospital stay, death in this study, and the independent multivariate analysis variables are those with p<0.20 in the bivariate analysis, having a proportional behavior. Remained in the final model the p < 0.05 variables.

In this analysis strategy a three hierarchical levels model was set, introducing stepwise variables, starting with the more distal variables and simultaneously introducing only variables in the same level. Thus, these variables can function e.g. as confounding factors for the proximal, and mediator for the distal factors.

Each variable effect on the outcome is interpreted as adjusted for the variables belonging to the hierarchically previous levels (more distal) and for the same level variable effects.

The first model level comprised the maternal biological features, as well as gestation-associated conditions, birth assistance and newborn gender. The second level consisted of newborn health and birth status. Proximally to the outcome, third level, neonatal assistance-related aspects were included (Figure 1).

The Stata version 9 software was used, and the 5% significance level adopted . This study was approved by the UNITAU Ethics Committee (EC), process 325/07.




HMD - hyaline membrane disease; PPV- positive pressure ventilation; PN - parenteral nutrition.

**Figure 1 – Hierarchical model death risk variables list for neonatal intensive care unit.**

## RESULTS

Between 2005 and 2007, 523 newborns were admitted to the TUH NICU, being 28 (5.4%) excluded due to transference. From the 495 newborns study group, 129 died (26.1%), 54% male and 46% female. The mean newborns stay length among those who were discharged was 19 days, while the mean stay length for those who died was 8 days, p<0.001.

These variables underwent survival analysis by the bivariate model and Kaplan-Meier curve. The survival curve is shown in figure 2; 50% of the deaths were seen up to the 10$^{th}$ hospital day. Later, the final result was obtained from the Cox multivariate model. No censored data were considered, as this possibility was prevented by excluding the children transferred to other services.

In the first level, the variables showing risk significance in the bivariate analysis were non-appropriate maternal age and prenatal steroids use. Meanwhile, cesarean delivery and multiple delivery were within the boundaries of risk factors significance. When hierarchized, the only factor re-

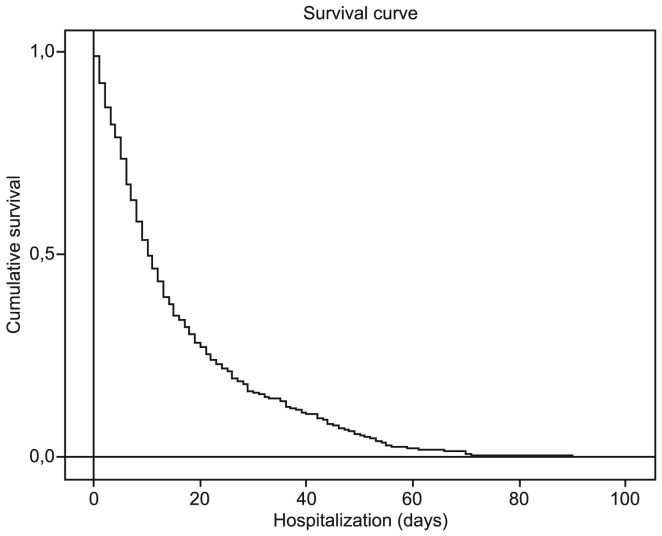



**Figura 2 - Survival curve for deaths identifying mean survival time, Taubaté, 2005-2007.**

maining in the model was maternal steroid therapy (Table 1).

In the second level, all variables were considered significant in the bivariate analysis, remaining in the final model congenital malformation, very low birth weight and 1st and 5th minutes Apgar score below seven (Table 2).

During immediate post-delivery assistance, third level, in the first analysis all variables were considered significant, remaining in the model as a risk factor intubation, and phototherapy as protective factor (Table 3).

Finally, were found maternal corticosteroid therapy, congenital malformation, very low birth weight, below seven/poor vitality 1st and 5th minute Apgar score, phototherapy (protective) and intubation (Table 4).

**Table 1 – Deaths and discharges rate for delivery, maternal age, maternal steroid use, hypertension, diabetes, multiple birth and gender for newborns staying in the neonatal intensive care unit**

| Variable (N)* | Discharge | Death | Total | P value |
|---|---|---|---|---|
| Delivery (486) | | | | 0.202 |
| Normal | 161 (77.4) | 47 (22.6) | 208 (100.0) | |
| Cesarean | 201 (72.3) | 77 (27.7) | 278 (100.0) | |
| Maternal age(470) | | | | 0.033 |
| Ideal | 216 (71.3) | 87 (28.7) | 303 (100.0) | |
| Non-ideal | 134 (80.2) | 33 (19.8) | 167 (100.0) | |
| Steroids (467) | | | | 0.02 |
| No | 313 (76.7) | 95 (23.3) | 408 (100.0) | |
| Yes | 37 (62.7) | 22 (37.3) | 59 (100.0) | |
| Hypertension(319) | | | | 0.257 |
| No | 168 (77.4) | 49 (22.6) | 217 (100.0) | |
| Yes | 73 (71.6) | 29 (28.4) | 102 (100.0) | |
| Diabetes (286) | | | | 0.653 |
| No | 209 (77.7) | 60 (22.3) | 269 (100.0) | |
| Yes | 14 (82.4) | 3 (17.6) | 17 (100.0) | |
| Multiple birth (491) | | | | 0.207 |
| No | 333 (74.5) | 114 (25.5) | 447 (100.0) | |
| Yes | 29 (65.9) | 15 (34.1) | 44 (100.0) | |
| Gender (491) | | | | 0.693 |
| Male | 203 (74.6) | 160 (25.4) | 272 (100.0) | |
| Female | 69 (74.0) | 59 (26.0) | 219 (100.0) | |

*N= total nr of newborns in each study variable. Values expressed as number (%).

**Table 2 – Deaths and discharges rate for the variables birth weight, 1st and 5th minute Apgar score, hyaline membrane disease, sepsis and congenital malformation, and gestational age for newborns staying in neonatal intensive care unit**

| Variable (N)* | Discharge | Death | Total | P value |
|---|---|---|---|---|
| Weight (491) | | | | <0.001 |
| ≥1,500 | 300 (86.7) | 46 (13.3) | 346 (100.0) | |
| Very low weight | 62 (42.7) | 83 (57.3) | 145 (100.0) | |
| Apgar 1min (478) | | | | <0.001 |
| Good vitality | 247 (83.7) | 48 (16.3) | 295 (100.0) | |
| Poor vitality | 107 (58.5) | 76 (41.5) | 183 (100.0) | |
| Apgar 5min (480) | | | | <0.001 |
| Good vitality | 319 (78.4) | 88 (21.6) | 407 (100.0) | |
| Poor vitality | 36 (49.3) | 37 (50.7) | 73 (100.0) | |
| HMD (495) | | | | <0.001 |
| No | 320 (80.4) | 78 (19.6) | 398 (100.0) | |
| Yes | 44 (46.8) | 50 (53.2) | 94 (100.0) | |
| Sepsis (491) | | | | 0.065 |
| No | 198 (77.7) | 57 (22.3) | 255 (100.0) | |
| Yes | 166 (70..4) | 70 (29.6) | 236 (100.0) | |
| Malformation (488) | | | | 0.002 |
| No | 318 (76.3) | 99 (23.7) | 417 (100.0) | |
| Yes | 42 (59.2) | 29 (40.8) | 71 (100.0) | |
| Gestation age (492) | | | | <0.001 |
| Full term | 127 (87.6) | 18 (12.4) | 145 (100.0) | |
| Preterm | 236 (68.0) | 111 (32.0) | 347 (100.0) | |
| Gestation age (492) | | | | <0.001 |
| Preterm | 295 (85.0) | 57 (15.0) | 348 (100.0) | |
| Very preterm | 67 (46.5) | 77 (53.5) | 144 (100.0) | |

HMD - hyaline membrane disease. *N= total nr of newborns in each study variable. Values expressed as number (%).

**Table 3 – Deaths and discharges rate for the variables VPP, NPP, intubation, cardiac massage, mechanic ventilation, phototherapy, venous access, and oxygen fraction for newborns staying in neonatal intensive care unit**

| Variable (N)* | Discharge | Death | Total | P value |
|---|---|---|---|---|
| PPV (479) | | | | 0.002 |
| No | 269 (77.5) | 78 (22.5) | 347 (100.0) | |
| Yes | 84 (63.7) | 48 (36.3) | 132 (100.0) | |
| PN (485) | | | | <0.001 |
| No | 197 (83.5) | 39 (16.5) | 236 (100.0) | |
| Yes | 159 (63.8) | 90 (36.2) | 249 (100.0) | |
| Intubation (479) | | | | <0.001 |
| No | 327 (81.4) | 75 (18.6) | 402 (100.0) | |
| Yes | 26 (33.7) | 51 (66.3) | 77 (100.0) | |
| Cardiac massage (479) | | | | <0.001 |
| No | 341 (75.8) | 109 (24.2) | 450 (100.0) | |
| Yes | 12 (41.4) | 17 (58.6) | 29 (100.0) | |
| Mechanic ventilation (485) | | | | <0.001 |
| No | 324 (76.4) | 100 (23.6) | 424 (100.0) | |
| Yes | 33 (54.1) | 28 (45.9) | 61 (100.0) | |
| Phototherapy(489) | | | | 0.112 |
| No | 180 (70.6) | 75 (29.4) | 255 (100.0) | |
| Yes | 180 (77.) | 54 (24.0) | 234 (100.0) | |
| Venous access | | | | <0.001 |
| No | 244 (86.2) | 39 (13.8) | 283 (100.0) | |
| Yes | 120 (57.4) | 89 (42.6) | 209 (100.0) | |
| IOF (493) | | | | <0.001 |
| 21% | 172 (83.9) | 33 (16.1) | 205 (100.0) | |
| Above 21% | 192 (66.7) | 96 (33.3) | 288 (100.0) | |

*N= total nr of newborns in each study variable. Values expressed as N(%). PPV- positive pressure ventilation; PN - parenteral nutrition; IOF - inspired oxygen fraction. Values expressed as number (%).

**Table 4 – Hazard ratio, p value and 95% confidence intervals of the hierarchical Cox model for the variables associated with death in neonatal intensive care unit, Taubaté, 2005-2007**

| Variable | HR | P value | [95% CI] |
|---|---|---|---|
| Prenatal steroids | 1.64 | 0.04 | 1.02 – 2.70 |
| Malformation | 1.93 | 0.029 | 1.05 – 2.88 |
| Very low birth weight | 4.28 | <0.001 | 2.79 – 6.57 |
| Apgar 1min < 7 poor vitality | 1.87 | 0.006 | 1.19 – 2.93 |
| Apgar 5 min < 7 poor vitality | 1.74 | <0.001 | 1.05 – 2.88 |
| Phototherapy | 0.34 | <0.001 | 0.22 – 0.53 |
| Intubation | 2.28 | < 0.001 | 1.41 – 3.70 |

HR - Hazard ratio; CI – confidence interval.

## DISCUSSION

The final result was based on hierarchical analysis, which allowed identifying the factors leading to increased first 28 days of life mortality, by approaching the outcome. With this method it was possible the exclusion of confounding variables and maintaining only pertinent variables.

Thus, it is known that at the distal level there is a close relationship between significant variables in the bivariate analysis – cesarean delivery, non-appropriate maternal age, multiple gestation and prenatal corticosteroid therapy – however remaining as the Cox model adjusted variable, only prenatal corticosteroid use.

This drug therapy aims lung function maturation, acting as a protective factor for mechanic ventilation and oxygen therapy.

Prenatal corticosteroids use is generally considered for women in risk of premature delivery or in other relevant clinical conditions such as preeclampsia, premature amniorhexis, placenta praevia, intrauterine growth restriction, among others, both maternal and fetal. However it should be emphasized that the maternal corticosteroid therapy benefits are observed in the 24-34 weeks of pregnancy range.[9]

The Rede Brasileira de Pesquisas Neonatais [Brazilian Neonatal Research Network] registered in 2004 that in 78% of the study treated pregnant women, this therapy was inappropriately given, leading the intended protective effects to eventually turn into harmful effects for the newborn.[10] Thus, inappropriate use may have been a reason for prenatal corticosteroid therapy appear in this study as a risk factor. The missing information on dosing time and doses may have contributed to this variable appearance as risk factor in our study. This is a possible study limitation.

In the second level, the group requiring more careful neonatal intensive care unit assistance is premature babies – particularly the very premature, their degree of immaturity and Apgar score and birth weight.[11]

The data regarding malformations in this study coincide with the literature. It is currently known that congenital malformation is an important concern for fetal death, first month of life death, and can itself increase the death odds.[12]

According to Amorim[13] in some world regions, particularly in developed countries, this cause overcomes prematurity. In the USA it was found that 45% of neonatal intensive care unit deaths were related to malformations, compared with 40% in this study.

Low birth weight and prematurity are universally acknowledged as the major neonatal mortality risk factors.[4] In this study, a significant association for very low birth weight – below 1,500 grams, was identified, 57%, in agreement with other studies showing that this group mortality is still very high in Brazil, specially in those below 750 grams[14] and far away from the rate in the best services, with about 10% mortality for very low weight infants.[15]

For the Araujo et al.[16] study, low birth weight is associated with unfavorable social-economic situation, making the newborn more vulnerable to conditions such as prematurity. Although the variable gestational age was out the hierarchical model, it is important to take into consideration its influence in the newborn initial clinical status, as it is known that the organs and systems maturation physiological response changes each single gestation week.[14]

According to Shrimpton[17], a mean 100 grams birth weight increase in a low birth weight newborn is associated with 30% to 50% neonatal mortality

rate change, showing the importance of programs aimed to improve maternal nutritional status.

It is still worthy emphasizing that neonatal mortality studies have found that the lower the fifth minute of life Apgar score, the lesser is the survival chance.[15] However, it is known that it is possible to see an Apgar score close to six in newborns from high risk pregnancies, cesarean sections or complicated births, being healthy premature babies, with a lower than in a full term baby muscle tonus.[18]

For this study it was found that poor vitality newborns – 5 minutes Apgar below 7 – had a 25% lower survival than those with good vitality – 5 minutes Apgar above 5. The same was seen for the 1 minute Apgar. It is generally found that an asphyxia full term baby has a 10% risk of death, and a neurological dysfunction risk of 10-45%. But, in a pre-term baby, the risks increased by 80% to 95%.[2]

It is exactly the initial newborn clinical severity that will influence the association of the third level variables identified, a reflex of previous levels as obstetric events, delivery and the birth assistance.

Variables as oxygen fraction above 21%, mechanic ventilation and DMH lost their significance in the hierarchical model. The explanation for this may be related to the NICUs ability to provide effective assistance for these infants.

Additionally, other variables in this level which weren't included in the final model could be confounded with increased mortality risk, because these children are clinically more severely ill, needing more specific interventional therapies, such as venous access, cardiac massage, VPP and NPP.

Phototherapy appeared as a protective factor; it was not possible to find an explanation for this; possibly, the longer hospital stay lead these infants to develop jaundice, in turn leading to phototherapy.

Additionally, the need of intubation in a newborn suggests clinical severity, being considered a mortality risk factor during NICU stay in this study.

Mortality risk evaluation by within variables correlation has been used in several countries, allowing to identify new and important factors such as low birth weight and prematurity, which were considered as important isolate variables.[14]

It was thus possible to identify risk factor associated with death in newborns staying in the Taubaté University Hospital neonatal ICU in the years 2005, 2006 and 2007, being these results comparable to others in literature reported populations. In addition, this model allowed hierarchically understanding the relationship between these factors in the causality of infant mortality, using a still seldom used study frame.

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**RESUMO**

**Objetivo:** Identificar fatores de risco associados ao óbito de recém-nascidos internados na unidade de terapia intensiva neonatal do Hospital Universitário de Taubaté, SP.

**Metodos:** É um estudo longitudinal com informações obtidas dos prontuários dos recém-nascidos internados na unidade de terapia intensiva neonatal, do Hospital Universitário da Universidade de Taubaté. A variável dependente foi o tipo de desfecho: alta ou óbito. As variáveis independentes foram variáveis maternas e gestacionais: idade materna, hipertensão, diabetes, terapia com corticóide e parto; variáveis do recém-nascido: peso ao nascer, duração da gestação, escore de Apgar no primeiro e quinto minutos de vida, nascimento múltiplo, malformações congênitas e sexo; variáveis relativas à internação: relato de ventilação mecânica, ventilação pressão positiva, relato de nutrição parenteral prolongada, sepse, entubação, massagem cardíaca, fototerapia, doença da membrana hialina, oxigênioterapia, tempo de internação e fração inspirada de oxigênio. Foi construído um modelo de forma hierarquizada em três níveis para análise de sobrevida, através do modelo de Cox; o programa computacional utilizado foi o Stata v9 e permaneceram no modelo final as variáveis com p<0,05. Os riscos foram estimados pela medida de efeito denominada *hazard ratio* (HR) com os respectivos intervalos de confiança de 95%. Foram excluídos do estudo os recém-nascidos transferidos durante a internação para outro serviço.

**Resultados:** Foram internados no período de estudo 495 recém-nascidos, com 129 óbitos (26,1%). No modelo final, permaneceram as variáveis uso de corticoterapia (HR 1,64; IC 95% 1,02-2,70), mal formação congênita (HR 1,93; IC 95% 1,05-2,88), muito baixo peso ao nascer (HR 4,28; IC 95% 2,79-6,57) e escores de Apgar menores que sete no1º min (HR 1,87; IC 95% 1,19-2,93) e no 5º min (HR 1,74; IC 95% 1,05-2,88) e as variáveis fototerapia (HR 0.34; IC 95% 0,22-0,53) e entubação traqueal (HR 2,28; IC 95% 1,41-3,70).

**Conclusão:** Foram identificados fatores basicamente ligados ao recém-nascido e à internação (exceto terapia com corticóide) destacando um possível fator protetor da fototerapia e o risco do recém-nascido com muito baixo peso.

**Descritores**: Mortalidade infantil; Unidades de terapia intensiva neonatal; Recém-nascido de baixo peso; Cuidados intensivos; Análise de sobrevida; Recém-nascido; Defeitos congênitos

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