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ORIGINAL ARTICLE

Epidemiology of prematurity and related comorbidities in very low birth weight preterm newborns

Juliana Cristina Vieira Gmack[1], João Victor Brincas Ramos[1], Paulyne Stadler Venzon[1], Regina Paula Guimarães Vieira Cavalcante da Silva[1]

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Abstract

Objective: To describe the major epidemiological features of prematurity, risk factors, prevalence of comorbidities, death and survival rates in very low birth weight newborns. **Methods:** Transversal study with rectrospective data collection from medical charts of 616 premature and very low birth weight newborns admitted to Complexo Hospital de Clínicas da UFPR (CHC-UFPR) between August 2008 and August 2018. It was studied comorbidities prevalence, survival rate and factors related to mortality. For all statistical tests, it was considered a 5% level of significance. **Results:** The average gestational age (GA) was 28.2 ± 2.9 weeks and the average birth weight (BW) was 997.4 ± 279.9 grams. The population with GA < 28 weeks (42.5%) had a greater need for neonatal resuscitation and ventilatory support and a higher prevalence of the following diseases: respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), pulmonary hypertension, pulmonary hemorrhage, peri-intraventricular hemorrhage (PIVH), retinopathy of prematurity (ROP), patent ductus arteriosus (PDA) and early-onset neonatal sepsis. The main comorbidities associated with an increased risk of death were (p <0.05): RDS (OR: 4,04), pulmonary hemorrhage (OR: 5,21) and PIVH (OR: 3,32). The reduction in survival rate was associated with lower values ??of GA and BW, as well as the presence of respiratory and neurological comorbidities. **Conclusions:** Extremely premature newborns have a higher prevalence of comorbidities and neonatal complications. Low birth weight, morbidities of the respiratory and neurological systems were the main factors associated with increased mortality.

[1] Universidade Federal do Paraná, - Curitiba - Paraná - Brazil.

Correspondence to:
Regina Paula Guimarães Vieira Cavalcante da Silva.
Universidade Federal do Paraná. Rua Quinze de Novembro, nº 1299, Centro, Curitiba, PR, Brazil. CEP: 80060-000. E-mail: reginavcs@uol.com.br

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INTRODUCTION

Prematurity represents the main cause of neonatal death and in children under five years of age, and its complications determine the death of more than one million newborns every year.[1,2] It is estimated that more than one in ten children are born prematurely around the world annually, and this incidence has increased in most countries in recent decades.[1,3] The largest portion of prematurity occurs in underdeveloped regions of the planet, mainly in sub-Saharan Africa and southern Asia.[3,4] Latin America and the Caribbean have prevalence rates slightly lower than the global trend, with 9.8% of premature births per year, although Brazil has a rate of 11.2% per year, ranking ninth among the countries with the highest absolute numbers of preterm births.[3]

In addition to resulting in a higher rate of infant death, prematurity is also associated with a higher incidence of several neonatal comorbidities; which, in addition to impacting survival, increases the risk of complications and their long--term consequences for health and quality of life for preterm newborns and their families.[5] Among the main associated comorbidities, we list respiratory diseases, such as respiratory distress syndrome (RDS) and bronchopulmonary dysplasia (BPD); cardiac changes, such as patent ductus arteriosus (PDA); neurological, such as peri-intraventricular hemorrhage (PIVH); and infections, such as neonatal sepsis and necrotizing enterocolitis (NEC).

Due to the high complexity and morbidity, premature birth also generates increased healthcare costs. In the United States of America, it is estimated that the cost of prematurity care is at least 26.2 billion per year, since premature newborns require, on average, nine times more days of hospitalization and require medical costs in the first year of birth life ten times higher than a child born at term.[6]

In newborns with birthweight (BW) below 1500g, prematurity results in even higher mortality and morbidity rates, requiring more specialized health care.[7,8] The epidemiological study of maternal, neonatal and healthcare characteristics related to prematurity and low birth weight enables a better understanding of risk factors related to these clinical conditions, promoting the improvement of healthcare for these children.

Therefore, the objective of this study was to describe the main epidemiological characteristics of prematurity in very low birth weight children treated in a tertiary hospital service over ten years, as well as the associated risk factors, prevalence of comorbidities, survival and death profile related to each of them.

METHODS

This is a cross-sectional study with retrospective analysis of data from medical records of very low premature newborns admitted to the Neonatal Intensive Care Unit (NICU) of the UFPR University Hospital Complex (CHC-UFPR) between August 2008 and August 2018. We considered the following inclusion criteria: gestational age (GA) < 32 weeks and BW < 1500g. Patients who presented congenital malformations, genetic syndromes incompatible with life and those who died within the first 24 hours of life were excluded from the study.

880 newborns cared for in the NICU were identified within the interval defined for the study, of which 773 met the inclusion criteria. Of these, 117 were excluded: 38 because they had some congenital malformation and/or genetic syndrome incompatible with life and 79 because they died within the first 24 hours of life. Therefore, the final sample included in the study involved 616 newborns.

The collected data was organized in Microsoft Excel® spreadsheets. For the statistical analysis, we employed Student's t test, Anova, Mann-Whitney test, Kruskal-Wallis Anova and Pearson's chi-square tests were applied. The cumulative probability of survival at 120 days was determined using the Kaplan-Meyer d method and the Gehan test. The multivariate logistic regression model was applied to estimate factors associated with mortality. For all tests, we considered a significance level of 5% (Statistica v.10.0 – Statsoft).

The project was submitted to the CHC-UFPR Ethics and Research Committee and approved under registration CAAE: 01372318.9.0000.0096.

RESULTS

Of the 616 very low birth weight premature newborns included in the study, 285 were male (46.3%) and 331 were females (53.7%). The average GA of the studied population was 28.2±2.9 weeks and the average BW was 997.4±279.9 grams; with 262 (42.5%) having a GA of less than 28 weeks and 354 (57.5%) with GA between 28 and 32 weeks. A small portion of the sample had a BW of less than 500 grams (2.1%); 130 with birth weight between 500 and 749.9g (21.1%); 171 between 750 and 999g (27.7%); 158 between 1000 and 1249g (25.6%) and 144 with birth weight > 1250g (23.4%). Both the group of newborns with GA < 28 and the group of newborns with GA ≥ 28 weeks had a predominance of being adequate for GA (AIG) classification (81.3% in both groups). Few newborns were classified as large for GA (LGA), with the highest frequency of 6.5% found among newborns < 28 weeks, and only 0.6% in the group with higher GA.

In the 1st minute, the frequency distribution of Apgar score < 4 was 48.6% for newborns with GA < 28 weeks and 27.5% for newborns with GA ≥ 28 weeks ($p < 0.001$) and in the 5th minute of 8.1 vs 2.8% ($p < 0.001$). The need for neonatal resuscitation (89.6% vs 71.3%, $p < 0.0101$) and the average length of stay (68 days vs 45 days; $p < 0.001$) were higher in newborns with lower GA. The temperature in the first hour of admission to the NICU was recorded in 506 newborns, with the average corresponding to 35.3ºC and 442 (87.3%) children had a temperature < 36.5ºC, of which, 341 had values < 36ºC (77 .1%), with no difference in the prevalence of hypothermia between the groups with GA shorter and longer than 28 weeks.

The main maternal characteristics, delivery room, hospitalization and neonatal comorbidities are presented in Table 1.

In children who developed late-onset sepsis and had a positive blood culture, coagulase-negative Staphylococcus was isolated in 151 (85.8%) patients. In the analysis by GA, this etiological agent was isolated in 84.1% of cases among newborns < 28 weeks, and in 88.9% among newborns ≥ 28 weeks (p=0.38).

Of the total number of patients included, 117 (19.0%) died; of which 88 (75.2%) had a GA < 28 weeks at birth.

Newborns weighing < 500g had a chance of death approximately 4 times higher than newborns weighing 500-749.9g [Odds Ratio (OR): 4.16, Confidence Interval (CI): 1.09-15, 86, p = 0.02], those weighing 500-749.9g; 3 times higher than those weighing 750-999g (OR: 3.15, CI: 1.88-5.27, p < 0.01) and these are 3 times higher than newborns weighing 1000-1249g (OR: 3.02, CI: 1.46-6.21, p < 0.01). There was no significant difference in the chance of death between newborns weighing 1000-1249g and children > 1249g (p = 0.44).

In the univariate analysis to determine morbidities predictive of death, BPD, necrotizing enterocolitis, PDA and PDA with surgical treatment did not obtain a significant p-value, while RDS, pulmonary hypertension, pulmonary hemorrhage, IVPH, IVPH grades III-IV and congenital pneumonia showed significance statistics (Table 2). Table 3 describes the predictive variables for death identified by the multivariate logistic regression model.

Table 4 brings together the 120-day postnatal survival rates calculated using the Kaplan-Meier method considering the variables of GA, BW and morbidities. In the population studied, a decrease in survival was observed from the fifth day of life, reaching around 90% on the tenth day and around 85% on the thirtieth, reaching 80% on the sixtieth and ninetieth day of life, respectively. The overall survival rate at 120 postnatal days was 75.3%. There was a lower survival rate among the most premature newborns (p < 0.001), as well as among those with lower BW (p < 0.001). The main diseases associated with reduced survival were: RDS (p < 0.001), IVPH (p < 0.01), pulmonary hemorrhage (p < 0.001) and pulmonary hypertension (p < 0.001).

DISCUSSION

The studied population showed a predominance of newborns classified as very premature and of very low birth weight. The frequency of children born weighing less than 500 grams was low, which may be related to the lower prevalence of births in GA considered borderline for viability or to the exclusion of cases of death in the first 24 hours of life – since children with extremely low weight have high mortality in the first 24 hours.[9,10] The French study EPIPAGE-2, published in 2015, corroborates these findings by showing an average survival of one day for extremely premature infants with a GA between 22 and 24 weeks.[9]

Approximately a quarter of the patients included in the study were born extremely premature. This population is subjected to more serious conditions at birth, higher death rates and worse prognoses upon hospitalization. The higher prevalence of 1st and 5th minute Apgar scores < 4 in these newborns reveals worse birth conditions and response to neonatal resuscitation compared to children with a higher GA. However, the values found in this study are lower than those found in other studies. Stensvold et al., in a Norwegian study with extremely premature infants, obtained a prevalence of 5th minute Apgar < 4 of 17.8%, more than double that found in the present study. This difference may be related to the population included in the Norwegian study, which limited the sample to newborns with GA between 22 and 26 weeks.[11]

Regarding maternal factors, the prevalence of chorioamnionitis was higher in newborns with GA < 28 weeks, an important cause of extremely premature birth. The present study found higher chorioamnionitis values compared to studies in developed countries. Anderson et al., in a study with extremely premature infants in California, United States of America, observed a prevalence of 13.7% for chorioamnionitis in this population.[12]

There was a greater need for resuscitation and orotracheal intubation in the delivery room for newborns under 28 weeks, which may be related to extreme prematurity. The average body temperature of newborns in the first hour of admission to the NICU was lower than appropriate, which would be between 36.5 and 37.5°C, according to the Brazilian Society of Pediatrics, which classifies temperature upon admission as an indicator of quality of care.[13] Studies show that hypothermia upon admission to the NICU is a predictor of mortality in premature newborns.[14,15] A study carried out in the Brazilian Northeast, which evaluated the occurrence of death in the first 24 hours of life in very low birth weight premature infants, obtained results similar to those of the present study, identifying that more than 80% of newborns had hypothermia upon admission to the neonatal unit, with more than 90% of those who died during this period.[10]

According to literature consensus, the lower the gestational age and birth weight, the greater the prevalence of comorbidities associated with prematurity.[16–19] In the present study, the prevalence of all diseases analyzed were higher in newborns < 28 weeks, with the exception of NEC, which predominated in the group > 28 weeks. One factor that could justify this finding is the proportion of newborns classified as SGA in the group > 28 weeks, which was approximately double that of the group < 28 weeks. The relationship between newborns classified as SGA and a higher risk of mortality and morbidities, including NEC, is well established in the literature.[20]

The overall survival was 75.3%, with a more pronounced decrease in the first days of life. This value was lower than the survival rate identified in studies involving international neonatal networks. A 2017 international study involving 10 neonatal networks with 88,327 very low birth weight prema-

Table 1. Maternal and neonatal characteristics according to gestational age.

Characteristics	< 28 weeks (n = 262)	> 28 weeks (n = 354)	*p*
Maternal age (years) n,%	26,8 + 7,5	27,8 + 7,1	0,10[1]
Gestational HS n,%	83 (32,3%)	160 (46,2%)	< 0,001[2]
Gestational *Diabetes Mellitus* n,%	23 (9,0%)	37 (10,7%)	0,58[2]
Premature Amniorrhexis n,%	71 (28,1%)	85 (24,9%)	0,44[2]
Corioamnionitis n,%	69 (29,1%)	40 (13,2%)	< 0,001[2]
Antenatal steroids n,%	224 (86,8%)	298 (84,9%)	0,58[2]
Twins gestation n,%	18 (60,0%)	23 (62,2%)	0,94[2]
C-Section delivery n,%	134 (51,3%)	283 (80,2%)	< 0,001[2]
Delivery room resuscitation n,%	232 (89,6%)	251 (71,3%)	< 0,001[2]
Tracheal intubation n,%	173 (74,6%)	100 (40,0%)	< 0,001[2]
Heart massage n,%	15 (6,5%)	13 (5,2%)	0,68[2]
Drugs used in resuscitation n,%	13 (5,6%)	13 (5,2%)	0,99[2]
MV use n,%	249 (95,4%)	222 (68,5%)	< 0,001[2]
Total MV time (days)[a]	12,5 (1-244)	5 (1 – 108)	< 0,001[3]
Surfactant use upon hospital stay n,%	205 (78,5%)	168 (47,6%)	< 0,001[2]
Total oxygen therapy time (days)[a]	45 (1-256)	12 (1-187)	< 0,001[3]
Pulmonary hypertension n,%	58 (22,2%)	26 (8,0%)	< 0,001[2]
Pulmonary hemorrhage n,%	34 (15,6%)	22 (8,3%)	0,01[2]
Acquired pneumonia n,%	16 (6,1%)	7 (2,2%)	0,02[2]
RDS n,%	230 (88,1%)	214 (66,0%)	< 0,001[2]
PDB n,%	87 (52,1%)	65 (24,0%)	< 0,001[2]
PIVH n,%	130 (57,5%)	96 (31,2%)	< 0,001[2]
PIVH grades III/IV n,%	60 (46,2%)	18 (18,8%)	< 0,001[2]
PRD n,%	78 (44,6%)	37 (14,1%)	< 0,001[2]
ROP with surgical treatment n,%	16 (11,3%)	2 (1,2%)	< 0,001[2]
PDA n,%	168 (64,4%)	124 (35,1%)	< 0,001[2]
NEC n,%	21 (8,0%)	30 (8,5%)	0,95[2]
Early sepsis n,%	141 (65,3%)	104 (53,6%)	0,02[2]
Late sepsis n,%	160 (75,5%)	132 (68,7%)	0,16[2]
Hospital stay duration (days) [a,b]	83 (1-263)	47 (1-188)	< 0,001[3]
Death n,%	88 (33,6%)	29 (8,2%)	< 0,001[2]

Note: [1]Anova *one-way*; [2]Pearson's Chi Square test; [3]Kruskal-Wallis test; Legend: HS = Hypertensive Syndrome; RDS = Respiratory Distress Syndrome; MV = Mechanical Ventilation; BPD = Bronchopulmonary Dysplasia; PIVH = Peri-intraventricular Hemorrhage; PRD = prematurity retina disease; PDA = Patent Ductus Arteriosus; NEC = Necrotizing Enterocolitis; [a]Variable described and median (minimum - maximum); [b]excluding the dead.

ture infants with a GA between 24 and 29 weeks indicated an overall survival of 87%[21]. Another German study published in 2019, which included 8,222 very low birth weight premature babies with a GA between 22 and 28 weeks, showed an overall survival of 86.6%.[22]

A significant association of reduced survival with reduced BW and GA was observed. Migoto et al. analyzed all live births in 2014 in the state of Paraná (Brazil) in a study that also identified BW less than 1000 grams and GA less than 32 weeks as risk factors for neonatal death[8]. Manuck et al. also reported an increase in survival with an increase in GA at birth in very premature children.[5] In extremely premature children, studies in other countries indicate that as GA increases, average BW and survival also increased.[11,12,23,24]

Respiratory and neurological comorbidities were the main ones identified as predictors of mortality. In agreement with these data, the survival rate was significantly reduced in the following comorbidities: RDS, pulmonary hemorrhage, pulmonary hypertension and PIVH. Similar results are found in other studies. Humberg et al., in Germany, identified the following factors as responsible for 71% of death cases, in decreasing order of prevalence: respiratory disorders (including RDS, BPD and pulmonary hemorrhage), sepsis, PIVH and NEC or focal intestinal perforation[22]. Manuck et al. found a similar

Table 2. Morbidities as predictors of mortality by univariate analysis.

Variables	Death with the variable	Death without the variable	*p*
PDA n,%	55 (18,8)	61 (18,9)	1[1]
PDA + Surgery n,%	2 (8,7)	53 (19,7)	0,27[2]
RDS n,%	108 (24,3)	8 (6,6)	< 0,001[1]
Pulmonary hypertension n,%	29 (34,5)	87 (17,4)	< 0,001[1]
Pulmonary hemorrhage n,%	36 (64,3)	59 (13,8)	< 0,001[1]
Congenital pneumonia n,%	36 (64,3)	59 (13,8)	< 0,001[1]
NEC n,%	13 (25,5)	103 (18,3)	0,28[1]
PIVH n,%	45 (19,9)	23 (7,5)	< 0,001[1]
PIVH III/IV n,%	28 (35,9)	40 (8,8)	< 0,001[1]
PRD n,%	3 (2,0)	5 (1,7)	1[2]

Note: [1]Pearson's chi-square test; 2Kruskal-Wallis ANOVA; Caption: RDS = Respiratory Distress Syndrome; BPD = Bronchopulmonary Dysplasia; PIVH = Peri-intraventricular hemorrhage; PDA = Patent Ductus Arteriosus; PDCA + Surgery = PCA carrying out surgical treatment; NEC = Necrotizing Enterocolitis.

Table 3. Morbidities as predictors of mortality by multivariate analysis.

Variables	OR	CI 95%	*p*
PDA	0,58	0.29 – 1.16	0.128
RDS	4.04	1.36-17.41	**< 0,001**
Pulmonary hypertension	1.95	0.91 – 4.10	0.08
Pulmonary hemorrhage	5.21	2.32 – 11.64	<0.001
Congenital pneumonia	3.16	0.60 – 13.19	0.134
NEC	1.87	0.63 – 4.93	0.230
PIVH	1.35	0.62 – 2.88	0.448
PIVH III/IV	3.32	1.47 – 7.68	**0.004**

Note: Multivariate logistical regression; Legend: RDS = Respiratory Distress Syndrome; PIVH = Peri-intraventricular hemorrhage PDA = Patent Ductus Arteriosus NEC = Necrotizing Enterocolitis.

pattern, observing that the most prevalent suspected etiologies in the population of premature infants who died were respiratory complications, hypoxic ischemic encephalopathy or severe PIVH and infection[5].

The direct relationship between RDS and increased mortality; however, is controversial, since several therapeutic options proven to be effective in the treatment of RDS are available for the management of this morbidity, including ventilatory support and administration of pulmonary surfactant. Furthermore, most of the cases that presented RDS and died also developed other morbidities, such as neonatal sepsis (84.2%), patent ductus arteriosus (47.2%), PIVH (38.9%), pulmonary hemorrhage (33.3%) and NEC (8.3%), which makes it difficult to identify RDS as a proven relevant factor in increasing the risk of death. Studies show that, in developed countries, very low birth weight neonates present other morbidities, such as pulmonary hypoplasia, severe PIVH and NEC, as the main causes of death in relation to RDS.[25]

Coagulase-negative Staphylococcus was the main agent identified in late neonatal sepsis. This finding corroborates literature data that points to it as one of the agents most related to neonatal sepsis. Late neonatal sepsis occurs predominantly in premature and very low birth weight children, with gram-positive bacteria being the main agents, and coagulase-negative Staphylococcus isolated in approximately half of the cases.[26] A Brazilian study in a large national tertiary hospital also identified coagulase-negative Staphylococcus. negative as the main agent of late neonatal sepsis, with emphasis on S. epidermidis.[27]

The recent study by the German Neonatal Network raised the hypothesis that the participation of centers in perinatal care networks is capable of increasing survival, especially in places where the initial survival rate of newborns is low. Lui et al., from an international cohort, also highlighted the importance of studies that describe the epidemiology and factors related to prematurity and its outcomes.[28] This study analyzed the outcomes of very premature and very low birth weight neonates in 11 countries and concluded that there was a significant increase in morbidities, mainly BPD, in almost all countries included, except Canada and Finland. The reduction in morbidity observed in Canada was greater than in all others, and the study suggests a possible relationship with the implementation of an evidence-based clinical practice protocol aimed at improving quality of care. In this case, the study suggests a possible association between the care practices adopted in neonatal units and the reduction of morbidities caused by prematurity, indicating it as an important focus for new studies.[28]

This study made it possible to assess the relationship between the mortality of very low birth weight premature newborns and gestational, perinatal and neonatal factors, especially comorbidities resulting from preterm birth that affect the respiratory system, infectious diseases and PIVH. Epidemiological studies that identify these factors are important to guide the implementation of scientifically based measures that provide a reduction, not only in mortality, but also in morbidities resulting from prematurity, which tend to increase with the improvement in the survival of extremely premature babies.

Table 4. 120-day postnatal survival rate.

Categories	Survival (%)	*p*
General	75,3	
By gestational age		
< 28 weeks	63,0	< 0,001
≥ 28 weeks	88,8	
By birth weight		
< 500g	23,1	
500-749,9	54,0	
750-999	78,9	< 0,001
1000-1249,9	83,4	
> 1250	95,3	
RDS		
Yes	70,8	< 0,001
No	88,1	
Infection		
Yes	74,6	0,95
No	83,1	
PIVH		
Yes	75,3	< 0,01
No	91,7	
PDA		
Yes	78,8	0,09
No	65,3	
Pulmonary hemorrhage		
Yes	34,1	< 0,001
No	81,4	
Pulmonary hypertension		
Yes	64,8	< 0,001
No	75,0	
NEC		
Yes	62,4	0,82
No	78,5	

Note: Kaplan-Meier Survival Analysis and Gehan's Test; Legend: RDS = Respiratory Distress Syndrome PIVH = Peri-intraventricular hemorrhage PDA = Patent Ductus Arteriosus NEC = Necrotizing Enterocolitis.

We conclude that the population studied over ten years in the NICU at CHC-UFPR was predominantly composed of very premature babies; 50.9% of which were of extremely low birth weight. Overall survival was 75.3%, being significantly higher in the group of newborns with GA ≥ 28 weeks (88.5%). The main comorbidities that were associated with increased mortality were pulmonary and neurological diseases. Lower GA and BW values significantly reduced survival. The low average body temperature of newborns upon admission to the neonatal unit may represent an additional risk in this population, as it is a well-established factor in the literature associated with increased mortality.

The main limitations of the study are retrospective data collection with analysis of medical records, having a relatively small sample compared to larger multicenter studies, and being restricted to just one care center. However, the study gathers data from all patients admitted to the NICU of a tertiary hospital who met the inclusion and exclusion criteria within a ten-year period. For this reason, it is capable of providing evidence on the impact of prematurity, low birth weight and the main neonatal comorbidities on newborn survival, reinforcing the importance of epidemiological studies in determining risk factors and quality of care.

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