Early death, morbidity and pharmacotherapy in extremely premature and very premature in neonatal intensive care units

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Abstract

Objectives: to evaluate the evolution of extremely preterm and very preterm infants admitted to neonatal intensive care units, regarding the use of ventilatory support, morbidities, medication use, death, survival and viability.

Methods: a non-concurrent cohort study, with 163 very premature and extreme newborns hospitalized in three neonatal intensive care units, during 2016 and 2017. A descriptive analysis of the data obtained from the medical records was performed. The outcomes studied were the use of ventilatory support, morbidities, medication use, death and causes of death. A survival curve was constructed and a viability limit was defined.

Results: in the study, 28.2% were extreme and 71.8% were very premature. In this order of subgroups, the need for mechanical ventilation was higher for the extremes (65.2% and 41.0%) and the main diagnosis was early sepsis (78.6% and 82.6). Off-label (60.5% and 47.9%) and off-license (25.3% and 29.0%) medications were used. Most deaths (57.8%) occurred between the extremes, mainly due to septic shock. Survival was lower for the lowest gestational ages and the limit of viability was between 26 and 27 weeks.

Conclusions: the main morbidities were from the respiratory system, with high use of off-label and unlicensed medications. Extremes had a greater demand for intensive care in addition to needing more drugs and progressing more to death.

Key words *Pharmacoepidemiology, Extremely premature infant, Critical care, Intensive care units, neonatal*

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Introduction

Prematurity is globally the main cause of death in children under five years of age. The same occurs in Brazil, with a concentration of over 60% of infant deaths in the neonatal period.[1]

The World Health Organization (WHO) defines preterm birth as that birth which occurs before 37 weeks of pregnancy.[2]Despite preterm newborns generally have typical complications of this population, some groups are more vulnerable than others. In a meta-analysis carried out in high-income countries, in the period from 200 to 2017, it was observed a high variation in the survival rate, which was low for the gestational age (GA) under 25 weeks, close to 25%. After 27 weeks, the survival rate increased to 90%, which demonstrates that survival increases with the GA.[3] In this context, it is understood that many preterm infants (28 weeks and less than 32 weeks) and extreme preterm infants (less than 28 weeks) are especially vulnerable due to the physiological immaturity that is notably increased in these groups.[4]

Furthermore, extreme prematurity also indicates higher association with neonatal complications and worse clinical outcomes compared to moderate preterm infants (32 weeks to less than 34) and late preterm infants (34 weeks to less than 37), which is reflected in high premature mortality rates, as well as hospitalizations, surgeries and use of medication.[5] The diverse associated morbidities, in addition to interfere in the response to intensive care, lead the pharmacological treatment for this population to be challenging, since most of medications routinely used have their prescriptions based on results of surveys focused on adults, which differ from children in several aspects, including the pharmacological response.[6] Given the above, drug treatment for this population is mostly empirical, characterized by the recurrent usage of off-label and unlicensed drugs. It is considered as off-label drugs those that target age, indication and way of administration diverge from what is authorized by the competent health agency, in this case the Food and Drug Administration - FDA. On the other hand, medications without registry, those contraindicated for neonatology (did not present safety or effectiveness), as well as compounding pharmacy preparations through medical prescription, or modified by professionals without FDA regulation,[7] were classified as unlicensed.

All of these characteristics indicate that the components of intensive care during preterm hospitalization are determinative for the outcome of these patients. This study aims to describe the demand for intensive care, the main morbidities, the drug use, the causes of that and the viability between extreme preterm infants and very preterm infants, besides building information that may contribute with the clinical practice based on evidence.

Methods

A cohort study, hospital based, part of the research "Premature Birth Cohort – Survival and morbidity in premature infants in Neonatal Intensive Care Units (NICU) in the municipality of Vitória da Conquista – BA: a non-concurrent cohort study". The studied hospital units served as an internship field for the medical residency program in pediatrics and neonatology, and possessed protocol for similar clinical practices.

All extreme premature and very premature infants hospitalized in NICUs were included in the study, from January 1, 2016 to December 21, 2017. The population was studied from the day of admission until 27 days of life.

The sample for the original study was obtained by convenience (n=400). However, the smaller sample size necessary to represent the premature infant population in the region was estimated in 384, considering the following parameters: infinite population size (datum in which it is not possible to estimate the total of preterm infants that would need neonatal intensive care), expected frequency of 50% (considering the multiple outcomes assessed), 5% precision and confidence interval of 95%. For the analysis of this article, a cutoff was made, using as sample preterm infants with GA between 22 and less than 32 weeks. Finally, 163 preterm infants remained in this study.

Data were collected by means of the analysis in the preterm infants' medical records, stored at the service of medical files and statistics of hospitals. The following major congenital abnormalities were used as exclusion criteria: complex congenital heart diseases, gastrointestinal tract atresia, abdominal wall defect, hydrocephaly, encephalocele and diaphragmatic hernia.

The tool used to perform the collection was an adapted questionnaire from the National Survey *Nascer no Brasil* (Born in Brazil).[8] Volunteer healthcare researchers under supervision of neonatologists were responsible for data collection, using a digital questionnaire with the use of tablets with Koobo Toolbox 1.4.8 software. Data collection of the main field occurred between June 2018 and May 2019.

The dependent variable was the evolution of preterm infants. The considered outcomes were the demand for intensive care, main morbidities and the use of medication. It was also assessed the occurrence of deaths in this population, and the period in which they occurred. The survival curves and viability curves for the evaluated groups were also calculated.

In order to obtain GA, it was preferably used the date of the last menstruation, followed by early ultrasound. In face of the impossibility of these findings, the assessment of physical and neurological signs of newborns was used, by means of the Capurro of New Ballard scales.

The analyzed variables were: sex (male; female), birth weight (low weight; very low weight and extreme low weight), Apgar test after the fifth minute (≥ 7; < 7), type of delivery (vaginal; cesarean), use of surfactant in the birth room (no;yes), use of surfactant in NICU (no;yes), cardiopulmonary resuscitation in the birth room (no; only ventilation with positive pressure ventilation (PPV); advanced resuscitation: positive pressure ventilation with cardiac massage and/or use of medication), time of mechanical ventilation during hospitalization (0 day; 1 to 5 days, six days or more), city of origin of the mother (Vitória da Conquista; another city) and place of birth and hospitalization (same hospital; different hospitals, in the same city; birth in another city or in transit). The neonates with z score of birth weight under –1.29 (percentile 10%), defined in agreement with the Intergrowth-21 curves, were considered small for gestational age, categorized in yes or no.[9]

The main diseases developed in the period of 27 days were also described, according to the preterm subgroups: apnea, early respiratory distress, necrotizing enterocolitis, neonatal jaundice, early sepsis, late sepsis and respiratory distress syndrome (RDS) or hyaline membrane disease (HMD).

The use of medications was obtained for the period of hospitalization in NICU, according to the GA subgroup. Each pharmaceutical specialty was registered under the generic name, pharmaceutical form and way of administration. Besides the specialties (drugs) all the daily doses prescriptions were registered, obtained as number of analysis the number of total prescriptions. The pharmacological classification was performed according to the Anatomical Therapeutic Chemical (ATC) classification, preconized by the WHO.[2] For the present study, we used the classifications of drugs concerning level 1 (anatomical) and level 2 (therapeutic). The drugs were also classified as off-label and unlicensed for the population according to Costa *et al.*,[7] with the use of the international database Drug Dex-Micromedex.[10]

The occurrence of death for extreme and very preterm infants, during the neonatal period (first 27 days of life) was described and categorized in yes and no. Furthermore, the deaths were distributed according to the time of occurrence after birth (early neonatal period if occurred within 6 days of life or less, and late neonatal if occurred from 7 to 27 days). The main death causes were also described: septic shock, multiple organ failure, respiratory distress syndrome (or hyaline membrane disease), acute renal failure and pulmonary hemorrhage.

In this research, the time of follow-up onset was the date of birth of each patient and the time of follow-up was until de 27th day of life or the occurrence of death. Since the follow-up was daily, the standard was ½ of the period for deaths occurring within less than 24 hours of life. In this way, patients were followed for different times and death was the censoring event. The survival curve was performed to demonstrate the time of survival, during follow-up, of the subgroups of GA under 32 weeks: 23 to 15 weeks, 26 to 27 weeks, 28 to 29 weeks and 30 to 31 weeks and the Log Rank test was calculated between these groups and neonatal death. The evaluation of viability limit corresponds to gestational age in which the newborn presents 50% or more of survival chance outside the womb, and for this evaluation, the previously described subgroups were also used.[11]

First, the descriptive analysis by means of absolute and relative frequencies was performed. In order to describe diseases in this population at the neonatal period, the incidence of each of them was calculated. For all these mentioned variables, the differences between the two gestational age groups were compared with the Pearson's chi square test or Fisher's exact test. Concerning the evaluation of drug use (total, off-label and unlicensed), descriptive data analysis were carried out by means of simple frequency distribution, using the total of dose prescriptions as an analysis unit. For the construction of the survival curve, the Kaplan-Meier nonparametric method was used, and, when presenting viability, a bar graph with the subgroups of GA under 32 weeks was created. The Stata version 15.0 software (Stata Corporation, College Station, USA) was used in data analysis.

The research was approved by the Research and Ethics Committee of the Multidisciplinary Health Institute of the Federal University of Bahia (CAAE:79450717.4.0000.5556).

Results

Of 163 preterm infants, gestational age varied from 23 weeks to less than 32 weeks, with 46 (28.2%) of extreme preterm and 117 (71.8%) very preterm, with a statistically significant difference between the groups. Among extreme premature infants, over half were of female sex (52.2%) and had extreme low birth weight (65.2%). The classification as low for gestational age in this subgroup was observed in 12.2%; the Apgar score of fifth minute was <7 in 22.7%, and 60.9% were born via vaginal delivery. It was observed the use of surfactant in birth room (39.5%), although it was more frequent in NICU (72.7%). Maneuver of resuscitation only with PPV was used in 52.2%, while 21.7% needed advanced resuscitation in the birth room. For the last two variables, a significant difference was observed between the groups. The percentile of patients that needed or not mechanical ventilation was almost equivalent between those who did

not use it (34.8%), those who used for 1 to 5 days (32.6%) and those who used for a period equal or higher than 6 days (32.6%) (Table 1).

Among the very preterm infants, most of the population was of male sex (51.3%), 18.8% presented extremely low birth weight, and 22.2% were classified as small for gestational age. In this subgroup, the Apgar score of fifth minute was <7 for 19.8% and 50.9% were born via vaginal delivery. It was observed that there was lower use of surfactant in birth room (32.4%) and NICU (49.1%) in this subgroup. The PPV as maneuver of resuscitation was performed in 42.7%, whilst only 7.7% needed advanced resuscitation in the birth room. The period of use of mechanical ventilation was distributed as: 59% did not use, 23.1% used between one and five days and 17.9% used for six days or more. The statistical analysis revealed significant differences (p<0.05) between preterm subgroups for some variables of interest: birth weight, use of surfactant in NICU, maneuver of resuscitation in the birth room, and use of mechanical ventilation (Table 1).

The city of origin of the mother was different from the city of hospitalization for 58.7% of extremely preterm infants and 46.2% of very preterm infants. Concerning the city of occurrence of birth, it was observed that 10.9% of the extremely preterm infants and 6.9% of the very premature infants were born in another city or in transit, and 17.4% and 17.9%, respectively, were born in the same city of the hospitalization, but in different hospitals. (Table 1).

For extremely premature infants, the main diagnoses during the period of hospitalization were early sepsis (78.6%), early respiratory distress (67.4%), when 53% was RDS. For the very premature infants, the main diagnoses were: early respiratory distress (86.3%), when 65.2% were due to RDS and early sepsis in 82.6%. It was observed a statistically significant difference for incidences of early respiratory distress (67.4% in extremely premature and 86.3% in very premature); and of necrotizing enterocolitis, with incidence in the extreme and very preterm infants of 8.7% and 0.8%, respectively (Table 1).

9845 doses of medication were prescribed, totaling 85 different types of drugs. For extremely preterm 7337 doses were prescribed, of which 3518 (47.9%) were off-label and 2125 (29%) were unlicensed.

For the first group, the most used pharmaceutical specialties were antiinfectives for systemic use (41.1%). Of the off-label, the antiinfectives for systemic use also predominated (64.1%). The most used group of unlicensed drugs used was the central nervous system agents (93.9%) (Table 2).

For the second group, the most used classes were also antiinfectives for systemic use (35.2%). Among the off-label, the very preterm infants had similar usage than the extremely preterm, the most used were antiinfectives for systemic use (64.7%). Concerning unlicensed drugs, the most used were those specific to the central nervous system (93.5%) (Table 2).

Within the study population, 26 deaths (56.5%) occurred between extremely premature and 19 (16.2%) between very premature, a statistically significant difference between the 2 subgroups. For the extremely preterm, most deaths (73.1%) occurred in the early neonatal period, whilst for the very preterm, most (52.6%) evolved to death in the late neonatal period (Table 3).

Concerning causes of death, the main ones among extremely preterm infants were Septic Shock (42.3%), Multiple Organ Failure and Respiratory Distress Syndrome (or Hyaline Membrane Disease), both with 15.4% of deaths. In the subgroup of very preterm infants, the main cause of death was also Septic Shock (47.4%), followed by Acute Renal Failure (15.8%) (Figure 1).

The survival over the days was lower for the lower GAs, with higher decreases in the early neonatal period (Figure 2A). When assessing the survival probability of each GA group, it was observed that the limit of viability of the study population was in the subgroup 26-27 weeks (Figure 2B).

Discussion

In this study, the intensive care to extremely preterm infants and very preterm infants occurred due to, mainly, the high incidence of morbidities related to the respiratory tract and early sepsis for both groups, and they demonstrated high usage of off-label and unlicensed drugs. A higher proportion of death occurrence was observed in the group of extremely preterm infants, caused mainly by Septic Shock, with more decreases in survival in the early neonatal period. The viability of the preterm infant study population stood between 26 and 27 weeks of GA.

The high demand for maneuvers of resuscitation demonstrated in this study is higher the lower the GA is, due to physiological immatureness observed in premature newborns, mainly in the earliest.[12] A cohort study carried out in Brasília-DF demonstrated higher results than those observed in this study, with prevalence of necessity of any maneuver of resuscitation in 89.8% of extreme premature,[13] with the exception that this increase probably occurred due to the differences in complexity of services. While the survey carried out in Brasilia was performed in only one service, with maternity and NICU in the same place, the current study involved two regional hospitals of reference that attend many babies from neighboring cities, with low access to professionals specialized in neonatology for resuscitation in birth rooms.

The mechanical ventilation is an intervention with potential to save lives for critical patients, although is

Table 1

Characerization of the study population. Preterm Birth Cohort, Vitória da Conquista - BA, 2016-2017.

Variables	Extremely premature (n=46)		Very premature (n=117)		*p*‡
	n	%	n	%	
Sex					0.691‡
Male	22	47.8	60	51.3	
Female	24	52.2	57	48.7	
Birth weight					<0.001‡
Low weight	0	0.0	26	22.2	
Very low weight	16	34.8	69	59.0	
Extremely low weight	30	65.2	22	18.8	
Small for gestational age					0.164‡
No	36	87.8	91	77.8	
Yes	5	12.2	26	22.2	
Apgar 5th minute					0.687‡
≥ 7	34	77.3	89	80.2	
< 7	10	22.7	22	19.8	
Way of delivery					0.249‡
Vaginal	28	60.9	59	50.9	
Cesarean	18	39.1	57	49.1	
Surfactant in birth room					0.405‡
No	26	60.5	73	67.6	
Yes	17	39.5	35	32.4	
Surfactantin ICU					0.008‡
No	12	27.3	56	50.9	
Yes	32	72.7	54	49.1	
Maneuver of resuscitation					0.005‡
No	12	26.1	58	49.6	
Only PPV*	24	52.2	50	42.7	
Advanced resuscitation†	10	21.7	9	7.7	
Mechanicalal ventilation (days)					0.018‡
None	16	34.8	69	59.0	
1 - 5	15	32.6	27	23.1	
≥ 6	15	32.6	21	17.9	
City of maternal origin					0.149‡
Vitória da Conquista	27	41.3	54	53.8	
Another city	19	58.7	63	46.2	
Birth and hospitalization place					0.693§
Same hospital	33	71.7	88	75.2	
Different hospital, same city	8	17.4	21	17.9	
Birth in another city or in transit	5	10.9	8	6.9	
Diagnosis during hospitalization					
Apnea	8	16.7	23	20.3	0.740‡
Early respiratory distress	31	67.4	101	86.3	0.006‡
Necrotizing enterocolitis	4	8.7	1	0.8	0.023§
Neonatal jaundice	12	26.1	34	29.0	0.704‡
Early sepsis	38	78.6	92	82.6	0.570‡
Late sepsis	7	15.2	31	26.5	0.125‡
Respiratory Distress Syndrome	30	53.0	62	65.2	0.157‡

*PPV = Positive pressure ventilation; † PPVaccompanied by cardiac massage and/or use of medications; ICU = Intensive Care Units;
‡ Pearson's chi square test; § Fisher's exact test. Table created only for valid data, being observed losses for some variables: Apgar 5th minute = 8 lost observations, Way of delivery = 1 lost observation, Surfactant in birthroom = 12 los2 observations, Surfactant in ICU = 9 lost observations.

Table 2

Use of medications according to the first and second levels of ATC drug classification, Premature Birth Cohort,Vitória da Conquista - BA, 2016 - 2017.

Anatomical and Therapeutic group*	Extremely premature						Very premature					
	Total		*Off label*		Unlicensed		Total		*Off label*		Unlicensed	
	n	%	n	%	n	%	n	%	n	%	n	%
Digestive system and metabolism	273	10.9	61	4.0	-	-	1626	22.2	424	12.0	-	-
Medications foracid gastric disorders	28	1.1	28	1.8	-	-	180	2.4	180	5.1	-	-
Medications for gastrointestinal disorders	8	0.3	8	0.5	-	-	186	2.5	186	5.3	-	-
Vitamins	230	9.2	18	1.2	-	-	1229	16.8	40	1.1	-	-
Blood and hematopoietic organs	26	1.0	-	-	18	2.8	176	2.4	-	-	101	4.8
Anti-anemic medications	18	0.7	-	-	18	2.8	101	1.4	-	-	101	4.8
Cardiovascular system	219	8.7	165	10.9	9	1.4	428	5.8	326	9.3	37	1.7
Medications for cardiac disorders	164	6.5	119	7.8	-	-	282	3.8	217	6.2	-	-
Diuretic medications	34	1.4	25	1.6	9	1.4	110	1.5	73	2.1	37	1.7
Antiinfective for systemic use	1032	41.1	973	64.1	6	1.0	2582	35.2	2275	64.7	-	-
Antibacterial for systemic use	812	32.4	762	50.2	6	1.0	2167	29.5	1894	53.8	-	-
Antifungal for systemic use	215	8.6	209	13.8	-	-	404	5.5	376	10.7	-	-
Nervous system	868	34.6	273	18.0	595	93.9	2381	32.4	394	11.2	1987	93.5
Anesthetics	205	8.2	205	13.5	-	-	277	3.8	277	7.9	-	-
Antiepileptic	118	4.7	8	0.5	110	17.4	285	3.9	28	0.8	257	12.1
Psychoanalytic	482	19.2	-	-	482	76.0	1724	23.5	-	-	1724	81.1
Respiratory system	68	2.7	41	2.7	-	-	122	1.7	86	2.4	-	-
Medication for obstructive diseases	20	0.8	20	1.3	-	-	78	1.1	77	2.2	-	-
Others	22	0.9	5	0.3	6	0.9	22	0.3	13	0.4	-	-
Total	2508	100.0	1518	100.0	634	100.0	7337	100.0	3518	100.0	2125	100.0

*In the table, medications that possessed representation of at least 2% in any of the subgroups were presented.

Table 3

Occurrence of death according to subgroups of gestational age and period after birth. Premature Birth Cohort, Vitória da Conquista - BA, 2016 - 2017.

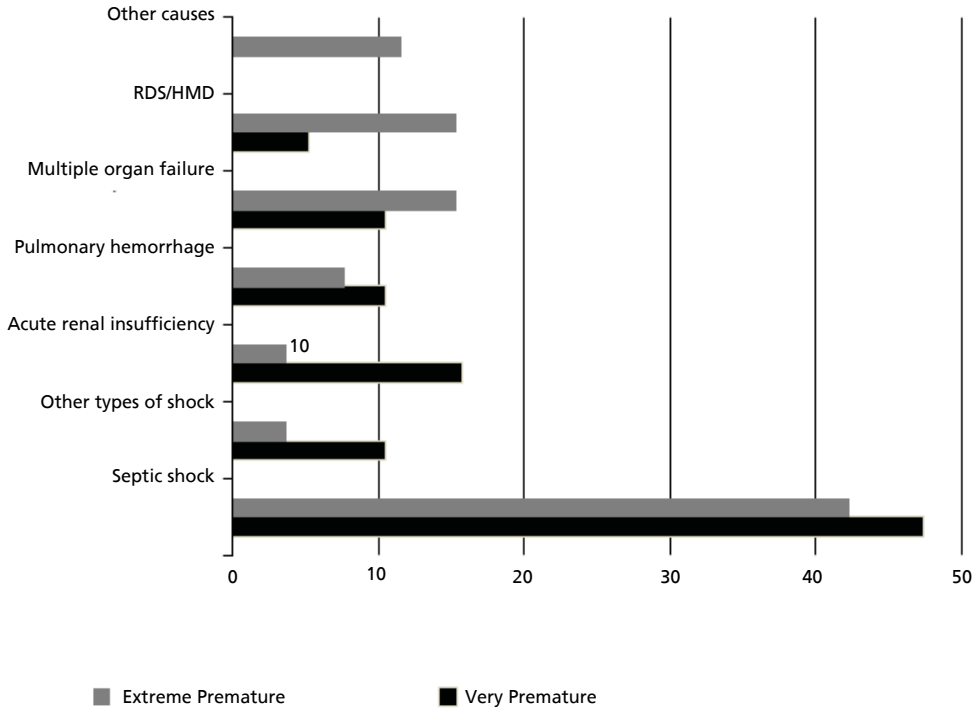
Variables	Extremely premature (N=46)		Very premature (N=117)		*p*
	n	%	n	%	
Deaths					<0.001*
No	20	43.5	98	83.8	
Yes	26	56.5	19	16.2	
	Extremely premature (N=26)		**Very premature (N=19)**		***p***
	n	**%**	**n**	**%**	
Death in the neonatal period					0.079*
Early neonatal	19†	73.1	9	47.4	
Late neonatal	7	26.9	10	52.6	

* Pearson's chi square test† Three deaths with less than 24 hours of life.

also associated with severe complications, this in part due to the fact that it is administered in patients with high risk of pulmonary or cardiac complications.[14] In this study, the need for mechanical ventilation was significantly higher among extremely premature, with at least 5 days of use in 32.6%. As a therapeutic tool, besides promoting mechanical breathing, this intervention protects the respiratory tract, decreases the respiratory muscle demand, allow the aspiration of secretions, among other benefits.[15] On the other hand, a recent systematic review demonstrated that the use of mechanical ventilation is associated with several deleterious effects of the

Figure 1

Main causes of death according to classification by gestational age. Premature Birth Cohort., Vitória da Conquista – BA, 2016 - 2017.



RDS = Respiratory Distress Syndrome; HMD = Hyaline Membrane Disease.

pulmonary function of newborns, including pulmonary bronchopulmonary dysplasia, pulmonary hemorrhage and pneumonia.[16]

Prematurity is considered a risk factor to receive a higher amount of medications per patient.[7]The higher use of medication may lead to higher risks, such as toxicity, adverse effects and drug interactions. In this study, a high use of off-label and unlicensed drugs was observed, probably, due to the clinical severity of the study population and the length of stay in NICU. However, according to the American Academy of Pediatrics, the therapeutic decision-making should always be guided by the best available scientific evidence and by the individual benefit for the patient, so that many times the off-label drugs are the best available therapy, since there are few gold-standard studies with this population.[17]

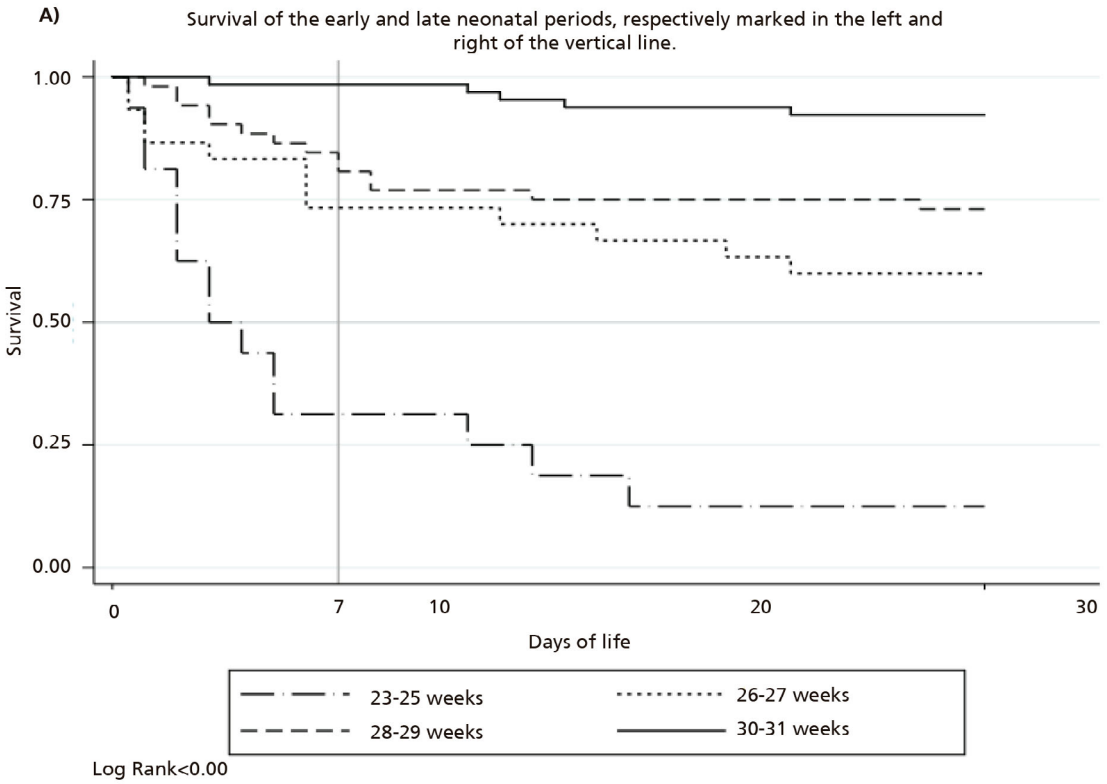
The antiinfectives for systemic use were the most used off-label group, both in extremely premature and very premature and the higher incidence of prescription (82.4%) were antibacterial drugs.This study agrees with the high incidence of early neonatal sepsis, for the preterm spontaneous labor may favor the colonization that generates the infection.[18] Also, it may favor the higher risk of late neonatal sepsis, which are frequently associated with the use of invasive devices, such as central venous catheter, mechanical ventilation and higher length of hospitalization.[19] Moreover, it is difficult to estimate clinical criteria for the sepsis diagnosis in these newborns, due to clinical instability, anatomical and functional immaturity, which may lead to the empirical use of antimicrobials in this population, based on susceptibility.[15]

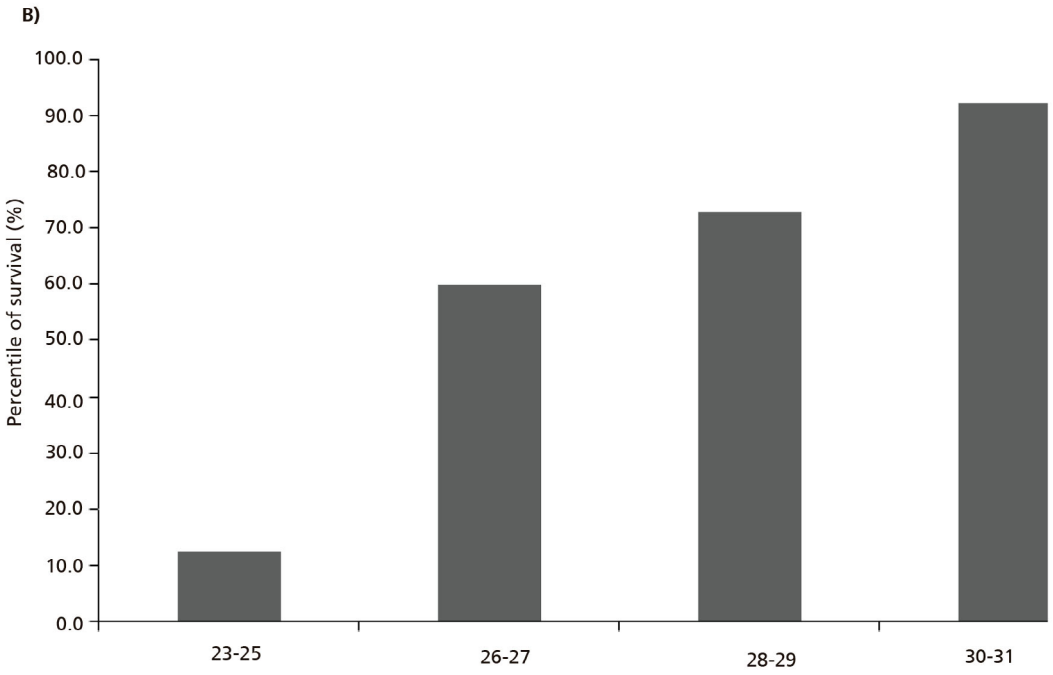
Caffeine was the most used unlicensed drugin this cohort. It is part of the psychoanalytic substances, which are good respiratory stimulators used in treatment and prevention of prematurity apnea, bronchopulmonary dysplasia and reduction of duration of mechanical ventilation.[19] This drug is in use for over 40 years, being one of the most frequently prescribed in the services of neonatal care.[20] Nevertheless, we highlight that the isolated use of caffeine cannot be considered as an unique intervention for these complications of neurodevelopment of premature infants. This is related to the extension in which apnea is responsible for delays in development and may be the primary causality or be associated with a context of other neurological sequels due to prematurity itself.

The occurrence of deaths observed in the neonatal period, both in extremely premature and very premature infants, was higher than that observed in another research conducted in Viçosa-MG, which registered a mortality of 47.5% and 13.8% for extremely premature and very premature, respectively.[21] Most extremely premature

Figure 2

Survival Curve (A) and Viability (B), according to subgroups of gestational age of extremely premature (23-25 and 26-27 weeks) and very premature (28-29 and 30-31 weeks), for the neonatal period. Premature Birth Cohort, Vitória da Conquista – BA, 2016 – 2017.





deaths occurred in the early neonatal period, and the respiratory conditions were important causes of these deaths. A similar result was verified by the National Institute of Child Health (NICHD), in the period between 2000 and 2011, which evaluated the causes and the moment of death in extremely premature infants. Most deaths in the first hours of life occurred due to immaturity and respiratory complications.

The survival percentile found in this study was crescent according to the advance of GA, with 12.5% of survival in the final of the neonatal period for preterm infants of 23-25 weeks and 92.3% for those with 31-32 weeks. In the subgroup of 26-27 weeks, a survival higher than 50% was demonstrated, the limit of viability for the study population. In developed countries such as the United States, however, which have lower mortality for this population, the limit of viability was estimated in 23 weeks of GA.[5] It is observed that premature infants in developing countries still suffer with conditions that could be avoided with relatively easy interventions, besides prenatal and perinatal care, such as qualification in maneuvers of resuscitation, prevention of hypothermia, algorithms for early detection of infections and early start of breastfeeding.[22]

The implementation of preconized measures by regulatory institutions, such as the organization of assistance in a regional and hierarchized way, investments in human and technological resources and improvement of assistance to birth is not yet a complete reality. The access to adequate obstetric and neonatal interventions has been demonstrating a great impact in the reduction of incidence of some aggravations and higher survival of newborns in risk.[23]

Some limitations were identified in this study, such as the use of a secondary database, documented in medical records, which is dependent on the quality of reports made by third parties, likely of information bias. Another aspect is the non-completeness of maternal, prenatal care and birth data, since the records used in collections were from the hospitalization of the newborn in the NICU, and, in many cases, this originated in other hospitals. In this way, some maternal data could be absent.

This study concludes that intensive care to extremely premature and very premature infants occurred, mainly, by virtue of the high incidence of morbidities related to the respiratory system and early sepsis, with high use of off-label and unlicensed drugs in the two subgroups. The occurrence of death was higher in the group of extremely premature infants, the most vulnerable group, caused mainly by Septic Shock. Preterm infants of lower gestational age had lower survival, with higher decreases in the early neonatal period, and the viability of the premature infants study population stood between 26 and 27 weeks of gestational age.

This study contributed with the establishment of guidelines directed to the improvement of care to the premature population, with subsidies to the planning and reinforcement of the mother-and-child care network. We highlight the relevance of investments in technical qualification for immediate care at birth and for adequate intra-hospital transport. These measures may lead to the reduction of morbidity and mortality, and, consequently, to the improvement of survival in more immature newborns.

Authors' contribution

Ferreira TS and Machado JS: conceptualization (Equal); Data curation (Equal), Formal analysis (Equal); Survey (Equal); Methodology (Equal); Visualization (Equal); Writing (Equal); Edition and Review (Equal).

Queiroz DB: data curation (Equal); Formal analysis (Equal); Methodology (Equal); Visualization (Equal); Writing (Equal); Edition and Review (Equal).

Costa RS: data curation (Equal); Formal analysis (Equal); Methodology (Equal); Visualization (Equal); Writing (Equal); Review (Equal).

Vieira VC: data curation (Equal); Formal analysis (Equal); Funding Acquisition (Equal) Methodology (Equal); Project Management (Equal); Supervision (Equal); Validation (Equal); Visualization (Equal); Writing (Equal); Edition and Review (Equal).

Lima RCG: data curation (Equal); Formal analysis (Equal); Funding Acquisition (Equal) Methodology (Equal); Project Management (Equal); Supervision (Equal); Validation (Equal); Visualization (Equal); Writing (Equal); Edition and Review (Equal).

Medeiros DS: conceptualization (Equal);data curation (Equal); Formal analysis (Equal); Funding Acquisition (Equal) Methodology (Equal); Project Management (Equal); Supervision (Equal); Validation (Equal); Visualization (Equal); Writing (Equal); Edition and Review (Equal).

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