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Evaluation of Survival and Neurodevelopment in Neonates Born Very Preterm at a Tertiary Centre in Portugal

Avaliação da Sobrevivência e Neurodesenvolvimento de Recém-Nascidos Grandes Prematuros num Centro Terciário em Portugal

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ABSTRACT

Introduction: Advances in medical care have significantly improved survival rates for preterm infants globally, leading to an increase of population of newborns at neurological risk. Knowledge of gestational age-specific outcomes is essential to guide and provide the best medical care. This study aimed to evaluate the impact of gestational age in mortality and neurodevelopment of very preterm infants. As a secondary objective, we aimed to determine the influence of perinatal factors on the combined outcome of neurodevelopmental impairment or death.

Methods: We conducted a retrospective cohort study of all infants born before completing 32 weeks of gestational age, admitted to the Neonatal Intensive Care Unit in a tertiary maternity hospital in Portugal from 2013 to 2021. Neurodevelopment was assessed at 24 months of corrected age, using Griffiths Mental Developmental Scales II. Moderate to severe neurodevelopment impairment was considered in the presence of at least one of the following criteria: global development quotient < 70, cerebral palsy, severe visual impairment or profound sensorineural deafness.

Results: There were 311 very preterm infants assessed for eligibility, 10.9% neonatal deaths and 11.9% losses to follow-up. Neurodevelopment evaluation was performed on 274 infants, of whom 6.2% (17/274) had moderate to severe neurodevelopment impairment: 7.5% (5/67) born before 28 weeks of gestational age and 5.8% (12/207) between 28 - 31 weeks. Global development quotient < 70 was verified in 4.7% of cases. Cerebral palsy was diagnosed in 3.3%, severe visual impairment in 0.7% and profound sensorineural deafness in 0.7%. The survival rate without moderate to severe neurodevelopment impairment exceeded deaths at 25 weeks and was > 86% from 28 weeks onward. In multivariable logistic regression analysis, gestational age was identified as a protective factor for moderate to severe neurodevelopment impairment or death (aOR 0.81; CI 95% 0.68 - 0.98), whereas male sex (aOR 3.19; CI 95% 1.57 - 6.71) and resuscitation with tracheal intubation (aOR 8.17; CI 95% 3.16 - 20.96) were independent risk factors.

Conclusion: This study reaffirms gestational age as a key determinant of survival and neurodevelopmental outcomes in very preterm infants, with those born before 28 weeks facing higher risks of mortality and severe neurodevelopmental impairments. Understanding local survival rates and neurodevelopmental outcomes is paramount for guiding perinatal decision-making and providing accurate evidence-based counseling to parents of preterm infants.

Keywords: Child Development; Infant, Extremely Premature; Infant Mortality; Morbidity; Neurodevelopmental Disorders; Premature Birth

RESUMO

Introdução: A melhoria dos cuidados perinatais tem contribuído para maiores taxas de sobrevivência, condicionando um aumento da população de recém-nascidos com risco neurológico. O conhecimento sobre os *outcomes* por idade gestacional é fundamental para guiar a prática clínica e prestar os melhores cuidados médicos. O principal objetivo deste estudo foi avaliar o impacto da idade gestacional na mortalidade e no neurodesenvolvimento dos recém-nascidos grandes prematuros. Como objetivo secundário pretendeu-se analisar os fatores perinatais que podem influenciar o *outcome* combinado de sequelas moderadas a graves do neurodesenvolvimento ou morte.

Métodos: Estudo observacional retrospetivo de uma coorte de recém-nascidos com menos de 32 semanas de idade gestacional, nascidos entre 2013 e 2021 num hospital de apoio perinatal diferenciado em Portugal. O neurodesenvolvimento foi avaliado aos 24 meses de idade corrigida utilizando a Escala de Desenvolvimento Mental de Griffiths II. Considerou-se a existência de sequelas moderadas/graves na presença de pelo menos um dos seguintes critérios: quociente global de desenvolvimento < 70, paralisia cerebral, cegueira ou surdez neurossensorial profunda.

Resultados: Foram incluídos 311 recém-nascidos; ocorreram 10,9% mortes neonatais e 11,9% perdas de *follow-up*. A avaliação do neurodesenvolvimento foi realizada em 274, dos quais 6,2% (17/274) apresentavam sequelas moderadas/graves: 7,5% (5/67) com < 28 semanas e 5,8% (12/207) entre 28 e 31 semanas. Verificou-se quociente global de desenvolvimento < 70 em 4,7%, paralisia cerebral em 3,3%, cegueira em 0,7% e surdez neurossensorial profunda em 0,7%. A taxa de sobrevivência sem sequelas moderadas/graves superou a mortalidade a partir das 25 semanas e, a partir das 28 semanas, foi superior a 86%. Na regressão logística multivariada, verificou-se que a idade gestacional foi um fator protetor (aOR 0,81; IC 95% 0,68 -0,98) para o desenvolvimento de sequelas moderadas/graves do neurodesenvolvimento ou morte, o sexo masculino (aOR 3,19; IC 95% 1,51 - 6,71) e a necessidade de reanimação profunda ao nascimento (aOR 8,17; IC 95% 3,16 - 20,96) foram fatores de risco independentes.

Conclusão: Este estudo comprova que a idade gestacional é um fator determinante para a sobrevivência e desenvolvimento de sequelas do neurodesenvolvimento, com maior risco abaixo das 28 semanas. O conhecimento destes dados por idade gestacional é fundamental para uma tomada de decisão baseada em dados locais, bem como para esclarecer os pais de prematuros.

Palavras-chave: Desenvolvimento Infantil; Lactente Extremamente Prematuro; Morbilidade; Mortalidade Infantil; Nascimento Prematuro; Perturbações do Neurodesenvolvimento

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KEY MESSAGES

- This study provides valuable insights into the follow-up of a substantial cohort of very preterm infants (88.1%) and is considered representative of the outcomes at our center.
- The survival rate without moderate to severe neurodevelopment impairment surpassed the mortality rate at 25 weeks of gestational age and exceeded 86% from 28 weeks onward.
- Abnormal neurodevelopmental outcome and death were associated with lower gestational age, male sex, and resuscitation with tracheal intubation.
- Understanding survival rates and neurodevelopmental outcomes by gestational age is crucial for supporting perinatal decision-making and guiding parental counseling in cases of preterm delivery within our unit.

INTRODUCTION

Advances in medical care have significantly improved survival rates for preterm infants worldwide,[1-5] with the most notable gains occurring in infants born under 28 weeks of gestational age (GA) – extreme preterm (EPT) infants.[6] It is described that the increased survival of EPT infants is accompanied by a higher incidence of morbidity.[5,7] However, in the last decade, there has been an improvement in both survival and survival without severe or moderate disabilities rates, despite the higher risk of neurodevelopmental impairment (NDI) in this group.[3] Most studies analyzed exclusively infants born EPT, with a gap in the literature regarding survival and neurodevelopment outcomes in very preterm (VPT) infants, born under 32 weeks of GA. In fact, VPT infants are also considerably affected – it is estimated that 30% - 40% have some degree of NDI.[3,8-10]

The factors that influence neurological development are complex, with brain maturation after the neonatal period being affected not only by biological factors but also by environmental and socioeconomic influences.[9,11,12] It is important to assess not only the survival rate but also the sequela and quality of life of those children who survived. Rates of survival with and without morbidities vary significantly between countries.[2] Survival rate without NDI at 2 - 2.5 years was 20% in the United States of America (USA) for infants born at 22 - 24 weeks (w) of GA and 34% and 42% in England and Sweden, respectively, for those born between 22 - 26 weeks.[3] Besides GA and birthweight (BW), the factors most strongly correlated with neurodevelopmental sequela include major brain injuries, such as severe periintraventricular hemorrhage and cystic periventricular leukomalacia (PVL), bronchopulmonary dysplasia, retinopathy of prematurity and sepsis.[13-16] Additionally, the increase in multiple pregnancies over recent decades has inherently contributed to a corresponding rise in prematurity.[17,18] However, the association between multiple births and neurodevelopmental outcomes is still controversial.[19,20]

Identifying children born preterm who are at risk of later development delay could enable targeted interventions, potentially preventing future disabilities, as a timely intervention could have a positive impact on cognitive outcomes in infancy.[3,21]

Understanding local survival rates and neurodevelopmental outcomes is essential for guiding perinatal decision-making and providing informed parental counseling in cases of extreme preterm deliveries.[2]

We aimed to evaluate the impact of GA in mortality and neurodevelopment in VPT infants. As a secondary objective, we aimed to determine the influence of perinatal factors on the combined outcome of neurodevelopmental impairment or death.

METHODS

Study design and patient selection

We conducted a retrospective cohort study of all preterm infants born before 32 weeks of GA admitted to the Neonatal Intensive Care Unit (NICU) in a tertiary maternity hospital from June 2013 to June 2021.

Neonates with major congenital malformations and/or chromosomal abnormalities were excluded.

An *a priori* power analysis, using an alpha error of 0.05 and a power of 95%, calculated that the minimum sample size would be 246 (201 without moderate to severe NDI and 45 with moderate to severe NDI or death).

Data collection

Clinical data were collected through the review of the perinatal and neonatal medical records using the NICU's database.

Prenatal and postnatal data

Collected maternal data included parity and sociodemographic characteristics, such as age and educational level (dichotomized as 'high': university degree or equivalent; or 'low': high school graduation or lower).

The perinatal factors evaluated included multifetal gestation, antenatal corticosteroid therapy for pulmonary fetal maturation (complete when either two doses of betamethasone or four doses of dexamethasone were administered),

cesarean or vaginal delivery, outborn status (infants born in other facilities and transported to our unit after delivery), sex, GA, BW, and endotracheal intubation during neonatal resuscitation.

Neonatal characteristics and morbidity were also explored. Small for gestational age (SGA) was defined as BW below the 10th percentile for GA by Fenton growth charts.[22] Neonatal sepsis was defined as clinical sepsis and abnormal laboratory findings (leukocyte count above 30 000/μL or under 5000/μL and C-reactive protein above 2 mg/dL), irrespective of blood culture results. Early-onset sepsis was considered when it occurred in the first 72 hours of life and late-onset sepsis when it occurred after 72 hours.[23] Bronchopulmonary dysplasia was defined as the need for oxygen at 36 weeks postmenstrual age.[24] Periventricular leukomalacia was considered when it was equal to or higher than grade II, according to the classification by De Vries *et al*.[25] Severe peri-intraventricular hemorrhage was considered if grade III or whenever hemorrhagic infarction was present, according to Volpe's classification.[26] Mechanical ventilation, postnatal surfactant, and corticosteroid administration were also assessed.

Follow-up data

According to the institution's protocol, all survivors are included for longitudinal follow-up at 24 months of corrected age (CA). This follow-up program is conducted by a specialized multidisciplinary team that includes pediatricians, nurses and trained educators. In this study we analyzed all infant's evaluation at 24 months of CA that met the inclusion criteria.

Neurodevelopment was assessed at 24 months of CA using the validated Griffiths Mental Developmental Scales II (GMDS-II). A global development quotient (GDQ) and development quotients for each specific area (locomotor, personal-social, hearing and language, eye and hand coordination and performance) were calculated.[27] The diagnosis of cerebral palsy (CP) was established according to the definition of the European Cerebral Palsy Network and the Global Motor Function Classification System, by an experienced neuropaediatrician.[28,29] Vision and hearing impairments were systematically evaluated by a pediatric ophthalmologist and otolaryngologist.

Moderate to severe NDI was considered in the presence of at least one of the following criteria: a GDQ for GMDS-II evaluation less than 70, diagnosis of CP, severe visual impairment (blindness) or profound sensorineural deafness requiring a hearing device.

Given that infants with severe perinatal complications have higher mortality rates and face a higher risk of adverse neurodevelopmental outcomes, we analyzed the combined outcome: moderate to severe NDI or death.

Data analysis

Statistical analysis was performed with IBM SPSS Statistics® version 29. Nominal variables were expressed as numbers and percentages. Variables were tested for normality using the Kolmogorov-Smirnov test. Depending on their distributions, numeric variables were reported as mean and standard deviation or median and interquartile

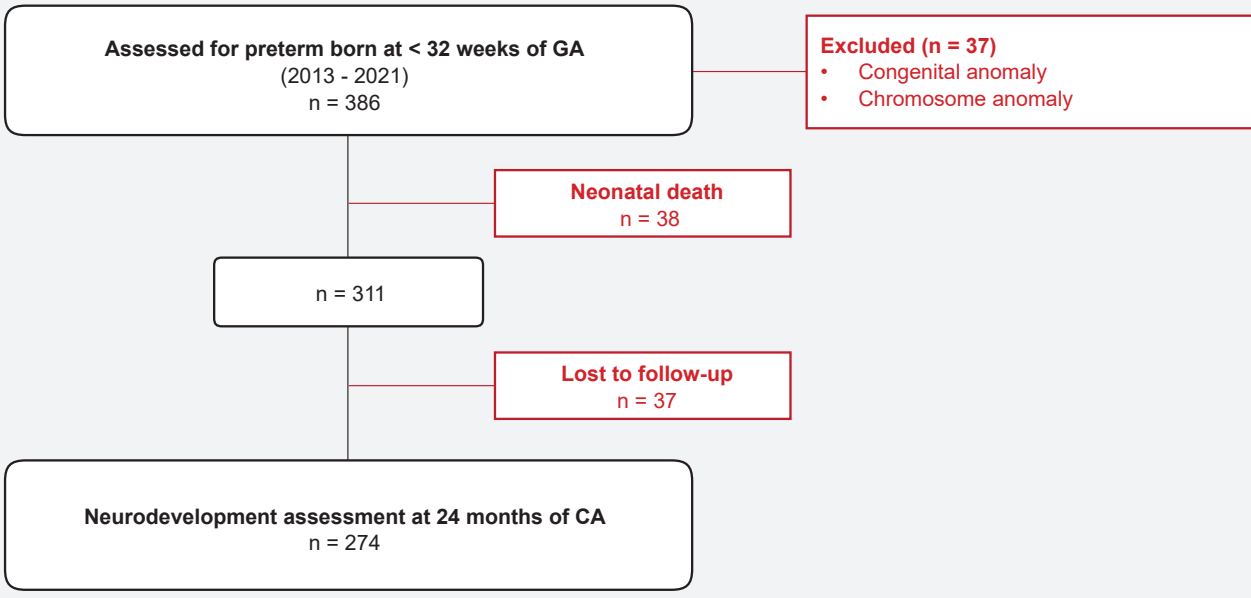


Figure 1 – Flowchart of patient selection
GA: gestational age; CA: corrected age

range (IQR). The χ^2 test or Fisher's exact test was used to compare nominal variables. Regarding quantitative variables, comparisons between groups were made using the non-parametric Mann-Whitney U test. The odds ratio (OR) and respective 95% confidence interval (95% CI) were presented as appropriate.

Adjustment by logistic regression was performed to identify the predictors for NDI. We constructed a model by adjusting for statistically significant and relevant maternal and perinatal factors, with the exclusion of variables with significant collinearity and with a very small number of cases. Quality of fit was verified by the Hosmer and Lemeshow test and the model was verified by the Omnibus test.

All reported *p* values are two-tailed with values inferior to 0.05 indicating statistical significance.

Approval was obtained from the local Ethics Committee (OBS_SF_192/2023).

RESULTS

During the study period, 311 VPT infants were assessed for eligibility. A flowchart illustrating the study's recruitment process is shown in Fig. 1. There were 38 (10.9%) neonatal deaths.

There were 37 (11.9%) losses to follow-up. When comparing the two groups (with and without follow-up) there were no statistically significant differences in GA ($p = 0.232$), BW ($p = 0.938$) and IMV ($p = 0.108$) – Table 1.

Global characterization

In this analysis, 274 children had neurodevelopmental assessments at 24 months of CA. The median GA was 29 weeks (IQR 2), with no sex predominance. The median BW was 1222 g (IQR 548) and 20% were SGA. Resuscitation with tracheal intubation was performed on 26%. During hospital stay, 42% needed invasive mechanical ventilation and the median of ventilation days was 1.5 (IQR 5.4).

Table 1 – Characteristics and comparison of infants with follow-up and lost to follow-up

Perinatal factors and morbidities	Infants with follow-up (n = 274)	Infants lost to follow-up (n = 37)	*p*-value	OR (CI 95%)
High educational level, n (%)	116 (44.8)	0 (0)		**0.55 (0.50 - 0.61)**[a]
Vaginal delivery, n (%)	110 (40.1)	14 (37.8)		1.10 (0.54 - 2.23)[b]
GA (weeks) (median | IQR)	29 | 2	30 | 2	0.232[c]	-
Twins, n (%)	82 (29.9)	6 (16.2)		0.57 (0.23 - 1.46)[b]
Monochorionic twins, n (%)	33 (40.7)	0		0.59 (0.50 - 0.71)[a]
TTTS, n (%)	5 (6.2)	0		0.94 (0.89 - 0.99)[a]
ACT, n (%)	232 (85.3)	35 (94.6)		3.02 (0.70 - 13.04)[b]
Outborn, n (%)	28 (10.2)	4 (12.5)		1.07 (0-35 - 3.23)[a]
Male, n (%)	140 (51.1)	19 (51.4)		1.01 (0.58 - 2.01)[b]
BW (gram) (median | IQR)	1222 | 548	1225 | 497	0.983[c]	-
SGA, n (%)	54 (19.7)	3 (8.1)		0.36 (0.11 - 1.21)[b]
Resuscitation with tracheal intubation, n (%)	72 (26.4)	6 (16.2)		0.54 (0.22 - 1.35)[b]
IMV, n (%)	114 (41.6)	10 (27.0)		0.52 (0.24 - 1.12)[b]
IMV duration (days, median | IQR)	1.5 | 5.4	3.0 | 0.5	**< 0.001**[c]	-
NIVM, n (%)	219 (79.9)	21 (56.8)		**0.33 (0.16 - 0.67)**[b]
Surfactant administration, n (%)	104 (38.0)	9 (24.3)		0.53 (0.24 - 1.16)[b]
Sepsis, n (%)	54 (20)	5 (14)		0.64 (0.24 - 1-71)[b]
BPD n (%)	21 (7.7)	1 (2.7)		0.34 (0.04 - 2.56)[a]
Severe PIVH, n (%)	21 (7.7)	1 (2.7)		0.33 (0.43 - 2.53)[a]
Cystic periventricular leukomalacia, n (%)	5 (1.5)	1 (2.7)		1.85 (0.20 - 17.05)[a]
Hydrocephalus needing derivation, n (%)	8 (2.9)	0		0.97 (0.95 - 0.99)[a]
Posnatal corticosteroids, n (%)	23 (8.4)	1 (2.7)		0.30 (0.04 - 2.31)[a]
Breastfeeding or mixed feeding at discharge, n (%)	224 (81.7)	19 (51.4)		**4.24 (2.08 - 8.67)**[b]

ACT: antenatal corticosteroid therapy; BPD: bronchopulmonary dysplasia; BW: birth weight; CI: confidence interval; GA: gestational age; IMV: invasive mechanical ventilation; IQR: interquartile range; PIVH: periventricular-intraventricular hemorrhage; NIMV: non-invasive mechanical ventilation; OR: odds ratio; SGA: small for gestation age.; TTTS: twin-twin transfusion syndrome. Bolded values are statistically significant ($p < 0.05$)
a: Fisher exact test; **b**: χ^2 test; **c**: Mann-Whitney U

Regarding comorbidities, sepsis was diagnosed in 20% (5% early-onset; 15% late-onset), bronchopulmonary dysplasia in 8% and severe peri-intraventricular hemorrhage in 8% of the infants. The remaining baseline characteristics are shown in Table 1.

Neurodevelopment assessment at 24 months CA

Neurodevelopment assessment revealed that 6.2% (17/274) of VPT infants had moderate to severe NDI: 7.5% (5/67) with GA < 28w and 5.8% (12/207) with GA 28 – 31 w. GMDS-II global development quotient < 70 was verified in 4.7% (12/274), with hearing and language being the most affected area. Profound sensorineural deafness was diagnosed in 0.7% (2/274) and severe visual impairment in 0.7% (2/274). Cerebral palsy was diagnosed in 3.3% (9/274): eight with spastic bilateral involvement and one spastic unilateral. The prevalence of CP was 4.5% (3/67) in GA < 28w and 2.9% (6/207) at GA 28 – 31w. Among the six patients born between 28 – 31w and diagnosed with CP, three had PVL and two had severe peri-intraventricular hemorrhage with hydrocephalus that needed derivation.

The overall survival rate and survival rate without NDI were inversely related to GA (Fig. 2). The survival rate without moderate to severe NDI exceeded mortality rate at 25 weeks of GA and was > 86% from 28 weeks onward (Fig. 2).

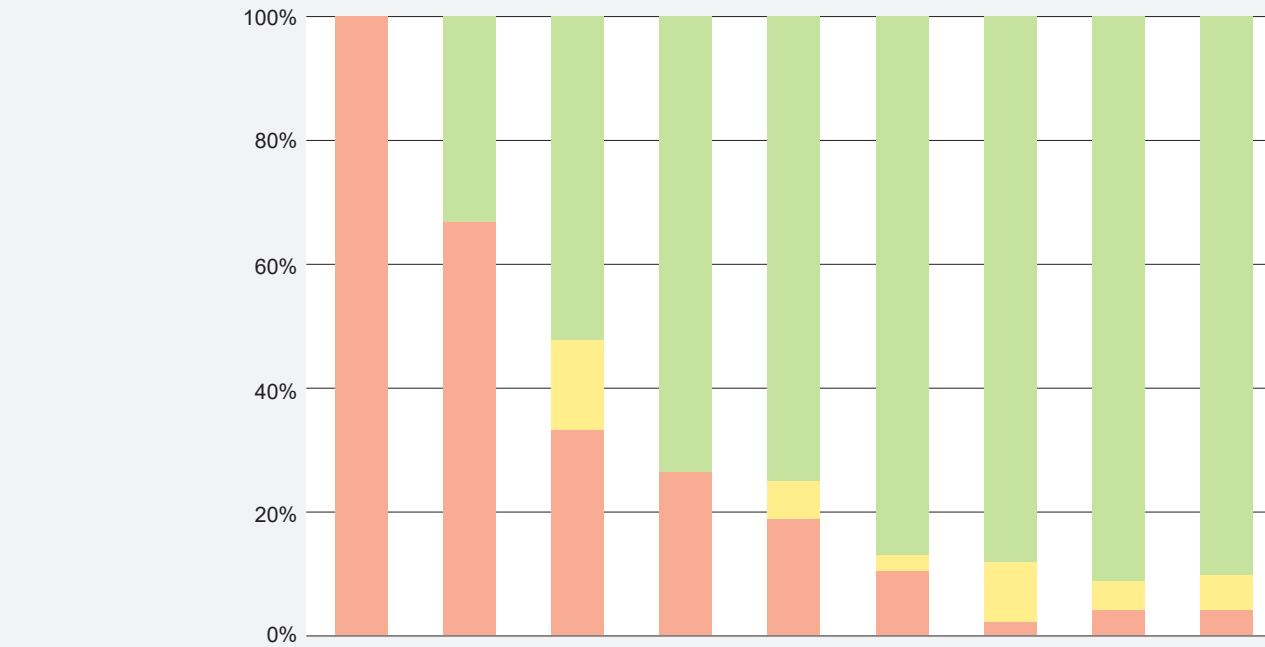
Impact of perinatal factors on the combined outcome of NDI or death

A comparison between the group with combined outcome of moderate to severe NDI or death with the group without NDI/death, showed statistically significant differences, as displayed in Table 2.

Multivariable logistic regression analysis was performed on the significant factors from the above analyzis and the model (p = 0.115) verified by the Hosmer and Lemeshow test was selected for further analysis, suggesting that the fitting condition of the model was good. After adjustment, (R^2 0.2), GA was a protective factor for moderate to severe NDI or death (aOR 0.81; CI 95% 0.68 - 0.98), whereas male sex (aOR 3.19; CI 95% 1.51 - 6.71) and resuscitation with tracheal intubation (aOR 8.17; CI 95% 3.16 - 20.96) were independent risk factors (Fig. 3).

DISCUSSION

Preterm infants are a vulnerable population at high risk of mortality, morbidity, and neurodevelopmental



GA (w)	23	24	25	26	27	28	29	30	31
Survival with no sequelae (n)	0	2	11	25	24	33	37	62	63
Survival with sequelae (n)	0	0	3	0	2	1	4	3	4
Deaths (n)	1	4	7	9	6	4	1	3	3

Figure 2 – Outcomes by gestational age (weeks)
GA: gestational age; w: weeks
Sequelae refers to moderate to severe neurodevelopment impairments

Table 2 – Characteristics and comparison between infants with combined outcome of moderate to severe NDI and death with the group without NDI/death

Perinatal factors and morbidities	Infants without moderate to severe NDI (n = 257)	Infants with moderate to severe NDI or death (n = 55)	*p*-value	OR (CI 95%)
Male, n (%)	127 (49.4)	40 (72.7)		**2.73 (1.44 - 5.19)**[a]
Maternal educational level – university degree, n (%)	131 (54.1)	12 (21.8)		**4.23 (2.12 - 8.42)**[a]
GA (weeks) (median | IQR)	29 | 2	27 | 2	**< 0.001**[b]	-
Twins, n (%)	78 (30.8)	15 (32.6)		1.01 (0.55 - 2.12)[a]
Monochorionic twins, n (%)	33 (42.9)	5 (35.7)		0.74 (0.23 - 2.42)[a]
Twin-to-twin transfusion syndrome, n (%)	5 (6.5)	3 (21.4)		3.93 (0.82 – 18.80)[c]
ACT, n (%)	218 (85.5)	42 (79.2)		0.648 (0.31 - 1.37)[a]
BW (grams) (median | IQR)	1230 | 540	925 | 550	**< 0.001**[b]	-
Vaginal delivery, n (%)	105 (40.9)	23 (41.8)		0.96 (0.53 - 1.74)[a]
Outborn, n (%)	28 (10.9)	5 (9.4)		0.85 (0.31 - 2.32)[a]
SGA, n (%)	50 (19.5)	5 (9.4)		0.43 (0 – 16 - 1.14)[a]
Resuscitation with tracheal intubation, n (%)	62 (24.2)	40 (75.5)		**9.63 (4.84 - 19.16)**[a]
IMV, n (%)	103 (40.1)	43 (81.1)		**6.43 (3.1 - 13.37)**[a]
NIMV, n (%)	203 (79.0)	30 (56.6)		**0.35 (0.19 - 0.65)**[a]
Surfactant administration, n (%)	93 (36.2)	33 (62.3)		**2.91 (1.58 - 5.36)**[a]
Sepsis, n (%)	49 (19.1)	10 (18.9)		0.99 (0.47 - 2.10)[a]
BPD, n (%)	10 (3.9)	2 (3.8)		0.99 (0.21 - 4.56)[c]
Posnatal corticosteroids, n (%)	21 (8.2)	2 (3.8)		0.44 (0.10 - 1.94)[c]
Severe PIVH, n (%)	18 (7.1)	20 (37.7)		**7.95 (3.82 - 16.55)**[a]
Cystic periventricular leukomalacia, n (%)	3 (1.2)	2 (3.8)		3.28 (0.54 – 20.14)[c]
Hydrocephalus needing derivation, n (%)	5 (1.9)	3 (5.7)		2.24 (0.2 - 15.4)[c]

ACT: antenatal corticosteroid therapy; BPD: bronchopulmonary dysplasia; BW: birth weight; CI: confidence interval; GA: gestational age; IMV: invasive mechanical ventilation; PIVH: periventricular-intraventricular hemorrhage; NDI: neurodevelopment impairment; NIMV: non-invasive mechanical ventilation; OR: odds ratio; SGA: small for gestational age.
Bolded values are statistically significant ($p < 0.05$).
a: χ^2 test; **b**: Mann-Whitney U test; **c**: Fisher exact test

impairments that carry lifelong consequences.[2,3,15,30,31] Some authors have shown an improvement in survival rates and sequelae-free survival in recent decades, however, these children are still at high risk of NDI.[3,32] Assessing neurodevelopment outcomes is important because of-its impact on the child's quality of life, especially in VPT. The gestational age-specific data and knowledge presented in our study is crucial for providing parents with accurate information regarding the risks of mortality and NDI in this group of newborns.

In our study, the mortality rate < 32 weeks GA was 10.9%. This is slightly higher than that reported in other studies and might be explained by the fact that we included deaths that occurred in the delivery room, which is not the case in other studies (eNewborn).[30] A previous Portuguese study analyzing the same age group reported a mortality rate of 15%.[33]

We observed a decline in mortality rates with increasing GA up to 28 weeks, after which mortality stabilized below 4% (Fig. 2). This trend is consistent with findings from the eNewborn European Network database study, which also includes Portuguese data.[30]

Our follow-up rate of 88.1% is higher than reported in other studies and close to the ideal value in this age group, as referred by the guidelines of the American Academy of Pediatrics (90%).[3,7,34] When comparing the two groups (with and without follow-up), there were no statistically significant differences in GA, BW and invasive mechanical ventilation. None of the infants lost to follow-up were born to a mother with higher education.

In our study, the survival rate without moderate to severe NDI exceeded the number of deaths at 25 weeks of GA. Similar data was reported in a 2006 study (EPICure).[32] Our survival rate without moderate to severe NDI improved with increasing gestational age, exceeding 86% from 28 weeks onward. The survival rate without NDI was higher

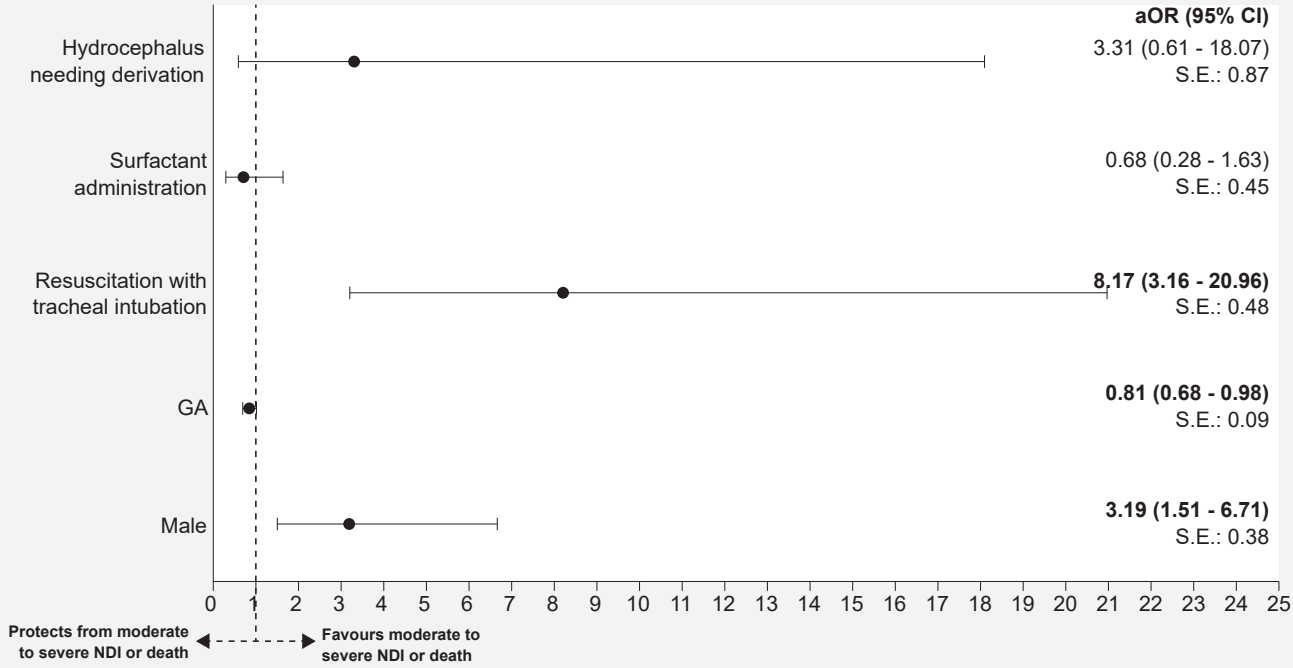


Figure 3 – Multivariate logistic regression including factors that may influence moderate to severe NDI or death
Variables included in multivariate logistic regression: male sex, gestational age, resuscitation with tracheal intubation, surfactant administration and hydrocephalus needing derivation.
aOR: adjusted odd ratio; CI: confidence interval; GA: gestational age; NDI: neurodevelopment impairment; SE: standard error.
Bolded values are statistically significant ($p < 0.05$).

in our study than what is reported in EPIPAGE for GA ≤ 26 weeks (67.8% *vs* 45.5%) but slightly lower at 27 – 31 weeks (87.6% *vs* 90%).[3]

Regarding NDI, in our study 6.2% of VPT had moderate to severe NDI at 24 months of CA, which is lower than the 10% reported in Resende *et al*, a Portuguese study conducted at the same hospital with similar methods but with inclusion of VPT and/or BW < 1500 g.[35] Comparison of GMDS-II GDQ < 70 and CP also revealed better results (GMDS-II GDQ < 70: 4.7% *vs* 6.8% and CP: 3.3% *vs* 6%), which can be justified by the continuous improvement of medical care.[35]

The EPICure study reported 13.4% of severe NDI in infants < 28 weeks of GA, while our group reports 7.5% for the same GA.[32] However, comparison with other studies regarding the presence of NDI must be done cautiously, since the methodology, scale applied and the population studied varied across different publications.

In our study, the incidence of CP (4.5% in GA < 28 w and 2.9% at 28 – 31 weeks) was lower than what is reported in the European CP surveillance program (14% at < 28 weeks of GA, 6% at 28 – 31 weeks and < 1% at 32 – 36 weeks).[6,28] However, it bears mentioning that the diagnosis of CP was performed in children with ≥ 5 years of age (*vs* 24 months CA in our study) which may lead to an underestimation of our results, as milder cases may not have been identified.

There are currently few studies in Portugal evaluating neurodevelopment in VPT. Furthermore, none of them are stratified by GA and neither analyzed the correlation with possible risk factors and serious mortality complications.

In our study, abnormal neurodevelopmental outcomes were associated with lower GA, male sex and resuscitation with tracheal intubation. Lower GA is well described to be associated with neurodevelopment impairment and mortality.[3,35-37] In our cohort, this was evident, with survival rates without serious sequela exceeding mortality rates at 25 weeks and being over 86% from 28 weeks of GA onwards. Since lower GA is related to a higher risk of morbidities, the literature is more centered in EPT, with limited studies regarding neurodevelopment outcomes in VPT.[1,5,7,38,39] Concerning sex, there are theories about males being more vulnerable to injury due to differences in brain organization and genetic or hormonal predisposing factors.[2,13,40,41] However, a systematic review that included studies conducted later in childhood, revealed that the influence of sex on general cognition was largely reduced at five years old.[41] Resuscitation with tracheal intubation at birth is related to a lower Apgar score, and in accordance to what is described in the literature, the need for advanced resuscitation at birth, in our study, was associated with moderate to severe NDI or

death.[37]

The aim of the evaluation of maternal education was to infer about the socioeconomic status, as it is described in the literature that a lower status is a risk factor for NDI.[3,4,7,41] In our study, the bivariate analysis showed that a higher level of maternal education was a protective factor for NDI. In a systematic review, unlike factors related to infant characteristics, the influence of parental education appeared to persist until middle childhood.[41]

A previous study in the same NICU found that fetal growth restriction was associated with a significantly increased risk of poor neurodevelopmental outcome at 24 months of CA, compared to infants with appropriate weight for GA.[42] However, in this study we only evaluated the weight percentile for GA and no differences were found. In the literature, there is often no clear definition of fetal growth restriction and sometimes SGA is used, which can confuse the results and make comparison difficult.

When comparing singletons to multiples, there were no differences in mortality and NDI, which is similar to the results reported in an Italian study and in a recent systematic review.[19,43] In contrast to Taborda *et al,* who reported that monochorionic twins had an increased risk of severe neurodevelopmental delay.[20] Current results can be related to better prenatal care with closer monitoring of twin pregnancies.

To our knowledge, this is one of the few and most recent Portuguese studies to show neurodevelopment at two years of age in this population, with stratification by GA. The low rate of children lost to follow-up and the fact that they were not significantly different from our cohort are this study's major strengths. Nevertheless, being a retrospective and single-centre study, our analysis carries some limitations, as the findings may not be representative of other NICUs. Memory and registration biases can be minimized in this study, since the data on this population is recorded in our NICUs database by some of the authors that report to a national level database (National Registry of Very Preterm Newborns) and is systematically recorded from birth to discharge.[30] Another limitation is that children's neurodevelopment is only monitored and assessed up to 24 months of CA, as some neurodevelopment disorders may appear later. Therefore, an evaluation at school age would be important.

CONCLUSION

This study reinforces GA as a key factor influencing survival and neurodevelopmental outcomes in VPT infants. Our findings reveal that preterm infants born before 28 weeks face significantly higher risks of mortality and severe NDI. Furthermore, from 25 weeks of GA onward, the survival rate without moderate to severe sequela surpasses the mortality rate. Even though these data demonstrate improvements in both survival and survival without disabilities, it remains essential to maintain systematic follow-up and conduct thorough neurodevelopmental assessments in preterm infants. Understanding local survival rates and neurodevelopmental outcomes is crucial for perinatal decision-making and parental counseling in cases of preterm delivery.

AUTHOR CONTRIBUTIONS

MCS, CC: Study conception and design, data collection, analysis and interpretation, drafting and critical review of the manuscript.

CLD: Study conception and design, data collection, analysis and interpretation, critical review of the manuscript.

AD, DF: Study conception and design, data interpretation, critical review of the manuscript.

AT: Study conception and design, data analysis and interpretation, drafting and critical review of the manuscript.

All authors approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in October 2024.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

PATIENT CONSENT

Obtained.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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