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ORIGINAL ARTICLE

Morbidity and mortality in newborns at the limit of viability in Spain: A population-based study☆

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Abstract
Introduction: Perinatal care in extremely immature newborns is a clinical and ethical problem of great importance for professionals and families, and requires that the available information on the chances of child survival is of the highest quality. The aim of this study was to determine the specific rates of survival at hospital discharge, and survival without major morbidity in newborns with a gestation age (GA) ≤ 26 weeks in Spain.
Patients and methods: We included live newborns ≤ 26 weeks admitted to the collaborating centres of the SEN1500 network (2004-2010). Outborn patients, infants who died in delivery room, and those with congenital anomalies incompatible with life were excluded.
Results: A total of 3,236 patients were included. GA specific survival was 12.5, 13.1, 36.9, 55.7, and 71.9% at 22, 23, 24, 25, and 26 weeks of GA, respectively. Survival without severe intracranial haemorrhage, periventricular leukomalacia, bronchopulmonary dysplasia, and/or retinopathy of prematurity was 1.5, 9.5, 19.0, and 29.9% at 23, 24, 25 and 26 weeks GA, respectively.
Conclusions: Survival without major morbidity in infants less than 23 weeks GA is exceptional, and scarce in newborns with 23 and 24 weeks GA. Infants ≥ 25 weeks GA have reasonable chances of survival and, in the absence of major malformations or other relevant complications, they should be offered active resuscitation and intensive care. The continuous updating of the results of individual centres is of utmost importance, as well as their comparison with the reference population-based results.

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PALABRAS CLAVE
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Toma de decisiones clínicas

Morbimortalidad en recién nacidos al límite de la viabilidad en España: estudio de base poblacional

Resumen
Introducción: La asistencia perinatal a recién nacidos (RN) extremadamente inmaduros constituye un problema clínico y ético de gran trascendencia para profesionales y familias, y hace necesaria una información actualizada de la máxima calidad acerca de las posibilidades de supervivencia del niño. El objetivo de este estudio fue conocer las tasas específicas de supervivencia al alta hospitalaria y de supervivencia sin morbilidad mayor conocida en RN con una edad gestacional (EG) ≤ 26 semanas en España.
Pacientes y métodos: Se incluyeron los RN vivos de ≤ 26 semanas que ingresaron en los centros colaboradores de la red SEN1500 (2004-2010). Se excluyeron los nacidos extramuros, los fallecidos en el paritorio y los que tenían malformaciones incompatibles con la vida.
Resultados: En total 3.236 pacientes fueron incluidos. La supervivencia específica por EG fue de 12,5, 13,1, 36,9, 55,7 y 71,9% a las 22, 23, 24, 25 y 26 semanas de EG, respectivamente. La supervivencia sin hemorragia intracraneal grave, leucomalacia periventricular, displasia broncopulmonar y/o retinopatía de la prematuridad fue del 1,5, 9,5, 19,0 y 29,9% a las 23, 24, 25 y 26 semanas, respectivamente.
Conclusiones: La supervivencia sin morbilidad mayor en menores de 23 semanas de EG es excepcional, y en RN de 23 y 24 semanas, muy baja. Los RN ≥ 25 semanas de EG tienen posibilidades razonables de supervivencia y, en ausencia de malformaciones mayores u otras complicaciones relevantes, se les debería ofrecer reanimación activa y cuidados intensivos. Es fundamental la actualización continua de los datos propios de cada centro y su comparación con los resultados poblacionales de referencia.

Introduction

Due to advances in obstetric and neonatal care, the number of infants born preterm and their survival rates have increased significantly in the past few decades. Lowering mortality without increasing morbidity and sequelae is one of the most important challenges faced by perinatal medicine, especially in the group with the GA: 22-26 weeks.

In this group of newborns, at the limit of viability, decisions regarding obstetric and neonatal care continue to be a clinical and ethical issue of great importance for professionals and families alike. Including the parents in the decision-making process when they so desire requires information of top quality, based on reliable up-to-date data on the probabilities of survival, and above all, of survival without major morbidity that could lead to adverse effects on development. These decisions are usually based on data from the centre in which the obstetric and neonatal care is provided. However, technical, and also cultural and social aspects, may contribute to the wide variability in outcomes that has been reported in different centres and countries.[1-6]

No previous studies in Spain have analysed GA-specific morbidity and mortality rates, as they usually report the overall outcomes for the entire group of newborns at the limit of viability. Furthermore, variations in operational definitions, along with the fact that all the data usually come from a single centre, make it hard to extrapolate results. Knowing the outcomes in a large area with a similar cultural and organisational environment could provide an ideal basis for decision making, as well as a useful reference for programmes devoted to the ongoing improvement of the quality of care.

The aim of this study was to know the GA-specific rates of survival at discharge, and of survival without known major morbidity in a large population-based cohort of neonates with GA ≤ 26 weeks in Spain.

Patients and methods

The Spanish database SEN1500 systematically collects and analyses the data of live very low birth weight (VLBW) infants born in or admitted to the network's participating centres in the first 28 days of life.[7] The present study analysed the data of live NB ≤ 26 weeks GA admitted to the centres in the 2004-2010 period. We excluded newborns with congenital malformations incompatible with life. Infants born out of hospital were also excluded due to the potential selection bias in transferred patients, and to the possible effects of the transfer itself on morbidity and mortality.

GA was estimated in weeks and days based on the date of the last menstrual period, obstetric parameters, and the prenatal ultrasound registered in the mother's record. Whenever necessary, the neonatologist estimated GA based on the physical examination of the newborn.

We defined advanced cardiopulmonary resuscitation (CPR) as the need for endotracheal intubation, chest compressions, or the administration of fluid or medications.

We defined major morbidity as the presence of one or more of the following: severe intraventricular haemorrhage (IVH) (Papile grades 3 and 4)[8]; white matter damage: cystic

periventricular leukomalacia and/or persistent diffuse hyperechogenicities; bronchopulmonary dysplasia (BPD) defined as oxygen dependency at 36 weeks postmenstrual age; necrotising enterocolitis (NEC) ≥ Bell stage 2[9]; early-onset bacterial sepsis and/or meningitis (positive culture < 72 h) or late-onset sepsis and/or meningitis (positive culture > 72 h); retinopathy of prematurity (ROP) ≥ stage 3[10], and/or treatment with laser therapy.

Statistical analyses were performed with SPSS-19 software (SPSS Inc., Chicago, IL).[11] Continuous variables were expressed as mean and standard deviation (SD) or median and interquartile range (IQR), and comparisons between groups were performed with the Student T-test or Mann-Whitney U test, as appropriate, or ANOVA or the Kruskal-Wallis test for more tha two groups comparisons. Qualitative variables were expressed as proportion (%), and the chi-square or Fisher's exact tests were used for comparisons. All the hypotheses were assessed using two-tailed tests, and a p value <0.05 was considered statistically significant.

The characteristics, quality control, and data confidentiality systems of this database have been described elsewhere.[7] The Investigation and Ethics Boards in each hospital had previously approved the protocol.

Results

In the period under study, a total of 19,482 VLBW newborns were registered in the SEN1500 database, of which 3,915 (20.1%) were infants with a GA of 22 to 26 weeks. The number of neonatal intensive care units (NICUs) that participated in the data collection ranged from 49 to 63, which we estimate comprehends approximately two thirds of all the VLBW newborns in Spain (based on data from the Instituto Nacional de Estadística [Spanish National Institute of Statistics]). The distribution of participating units was as follows: level I (<50 VLBW newborns admissions/year): 72%; level II (50-100 admissions/year): 18%; and level III (>100 admissions/year): 10%.

In terms of being born in or out of hospital, 3,518 patients were inborn (89.9%) and 397 outborn (10.1%). After excluding infants with congenital malformations incompatible with life, a total of 3,377 patients were included in the study. Table 1 shows the demographic and somatometric characteristics of the patients by GA, along with data on prenatal care and some obstetric interventions.

Table 2 shows vitality at birth based on the Apgar score, as well as resuscitation interventions. Severe neonatal depression and the need for CPR decreased progressively as GA increased. Nevertheless, some of the most premature infants were not resuscitated as a result of limitation of diagnostic and therapeutic effort (LDTE) decisions. Among patients who required epinephrine during resuscitation (n = 199), survival was lower than in those who did not need it (37.7% vs. 62.3%; p < 0.001), and survivors (n = 75) presented major brain damage (MBD) more frequently (severe IVH and/or white matter damage) (7.9% vs. 3.5%; p < 0.001). We observed similar results in patients who required chest compressions (n = 264) versus those who did not, with survival rates of 34.1% vs. 65.9% (p < 0.001). MBD among these survivors (n = 90) was 10.3 vs. 4% (p < 0.001).

A high proportion of patients were admitted with a temperature below 36.5 °C (85.8%), and although it decreased significantly as GA increased, at 26 weeks it still affected over 80% of them. Finally, more mature infants had a lower risk index, based on the Clinical Risk Index for Babies score,[12] as well as a lower mortality rate in the first 24 hours of life (Table 2).

Table 3 shows the incidence of respiratory distress syndrome and patent ductus arteriosus, along with some clinical practice indicators and some of the observed complications. Figure 1A shows survival with and without BPD.

The proportion of patients with at least one brain ultrasound following admission to the NICU was 90.7%, ranging from 50% in patients with a GA of 22 weeks to 92.8 and 93.6% in those with a GA of 25 and 26 weeks (p < 0.001), respectively. The incidence of severe IVH decreased progressively from 23 to 26 weeks GA, with a percentage of 31.2%, 25.1%, 22.8%, and 17.9%, respectively. Some type of white matter damage was detected in 8.8% of patients, without significant differences by GA. GA-specific survival without MBD is shown in Figure 1B.

Out of the 1,796 patients that survived, 1,690 (94.1%) underwent a retinal examination before being discharged or transferred. Among them, 279 (16.5%) had ROP ≥ stage 3, and 289 (17.1%) were treated with laser therapy. Figure 1C shows the GA-specific survival without BPD, MBD, ROP and/or laser therapy.

The incidence of NEC was 13.3%, without significant differences by GA. Surgical treatment was required for 254 patients (7.8%). Focal gastrointestinal perforation (FGIP) was observed in 184 children (5.7%).

On the other hand, 226 newborns (7.0%) had early-onset sepsis, and 1,635 (50.5%) at least one episode of late-onset sepsis, with *Staphylococcus epidermidis* being the most frequent infectious agent (29.3%). Fungal infections were found in 287 patients (8.9%). Figure 1D shows the GA-specific survival without major morbidity.

GA-specific survival increased with increasing GA: 3.2% (22 weeks), 10% (23 weeks), 35.8% (24 weeks), 54.8% (25 weeks) and 71.2% (26 weeks). Table 4 shows the GA-specific survival for newborns admitted to the NICU. It also shows the mean hospital stay of patients who were discharged home, as well as their weight and head circumference at discharge. Mortality decreased progressively from 22 (87.5%) to 26 (28.1%) weeks of GA (p < 0.001), with death ocurring at a median (interquartile range) of 5 (1-15) days, and taking place significatively earlier among more immature patients: 2 (0-13) days, 3 (1-10) days, 5 (2-12.25) days, 6 (2-16) days, and 6 (1-22) days, from 22 to 26 weeks, respectively (p < 0.001). Of all patients, 58.2% died the first week, and 86.5% in the first 28 days.

Discussion

This is the first population-based study conducted in Spain on GA-specific survival and survival without a known major morbidity in newborns at the limit of viability. The overall survival of this large cohort of patients ≤ 26 weeks GA, which is representative of most Spanish communities, was 55.5%, similar to the reported rates in other developed countries. [3-15]

Table 1 Demographic and somatometric characteristics.

Characteristics	22 weeks	23 weeks	24 weeks	25 weeks	26 weeks	Total
Total live newborns	31	261	728	1,045	1,312	3,377
Delivery room death, n (%)	23 (74.2)	62 (23.8)	34 (4.7)	16 (1.5)	6 (0.5)	141 (4.2)
Admitted alive to the NICU	8	199	694	1,029	1,306	3,236
BW (g), mean ± SD (range) [a]	n = 8; 600 ± 104 (485-780)	n = 199; 609 ± 87 (400-920)	n = 694; 676 ± 98 (413-1,030)	n = 1,029; 759 ± 129 (350-1,310)	n = 1,306; 864 ± 154 (340-1,410)	n = 3,236; 774 ± 156 (340-1,410)
Length (cm), mean ± SD (range) [a]	N = 6; 30.5 ± 2.3 (28.0-34.0)	N = 145; 30.2 ± 2.2 (22.0-40.0)	n = 560; 31.5 ± 2.0 (22.5-40.0)	n = 869; 32.8 ± 2.2 (21.2-43.0)	n = 1,162; 34.1 ± 2.3 (20.0-45.0)	n = 2,742; 32.9 ± 2.5 (20.0-45.0)
HC (cm), mean ± SD (range) [a]	n = 4; 20.5 ± 2.0 (18.5-23.0)	n = 143; 21.3 ± 1.5 (18.0-27.0)	n = 570; 22.2 ± 1.5 (19.0-34.0)	n = 875; 23.0 ± 1.6 (18.0-34.0)	n = 1,172; 24.0 ± 1.6 (19.0-36.0)	n = 2,764; 22.2 ± 1.8 (18.0-36.0)
Male sex, n (%)	5 (62.5)	118 (59.3)	409 (58.9)	567 (55.1)	688 (52.7)	1,878 (55.2)
Ethnicity, n (%)						
White	6 (85.7)	142 (82.1)	497 (82.1)	765 (85.8)	1,015 (88.3)	2,425 (85.8)
Gipsy	0	6 (3.5)	17 (2.8)	21 (2.4)	23 (2)	67 (2.4)
Black	0	6 (3.5)	23 (3.8)	26 (2.9)	21 (1.8)	76 (2.7)
Asian	0	1 (0.6)	10 (1.7)	9 (1)	7 (0.6)	27 (1)
Latin American	1 (14.3)	17 (9.8)	53 (8.8)	58 (6.5)	60 (5.2)	189 (6.7)
Unspecified	1 (14.3)	27 (13.6)	94 (13.5)	150 (14.6)	180 (13.8)	452 (14.0)
Multiple pregnancy, n (%)	1 (12.5)	67 (33.7)	207 (29.8)	306 (29.8)	364 (27.9)	945 (29.2)
Prenatal care, %	87.5	79.5	85.3	86.5	88.1	86.5
Prenatal corticosteroids (at least one dose), %	57.1	58.8	80.3	84.8	85.8	82.6*
Chorioamnionitis, n (%) [a,b]	-	55 (43.3)	254 (39.0)	383 (37.9)	523 (29.1)	1,217 (34.5)**
Caesarean delivery, %	37.5	17.6	35.6	46.5	58.0	47.0*

SD: standard deviation; HC: head circumference; BW: birth weight; NICU: Neonatal Intensive Care Unit.

[a] N: total number of patients with available data included in the calculations.

[b] The history of maternal chorioamnionitis started to be recorded systematically in the database in 2008.

*$p < 0.001$.

**$p = 0.007$.

Table 2 State at birth, resuscitation in the delivery room, temperature at admission in the Neonanal Intensive Care Unit, Clinical Risk Index for Babies, and mortality in the first 24 hours post-birth.

	22 weeks	23 weeks	24 weeks	25 weeks	26 weeks	Total
Apgar ≤ 3, n [a]	8	196	683	1,019	1,292	3,197
*At one minute, %**	62.5	44.9	31.1	25.6	22.3	26.7
*At 5 min, %**	25.0	17.6	6.3	3.8	3.9	5.3
CPR, n [a]	8	197	694	1,027	1,304	3,230
Oxygen, %	100	86.3	94.5	93	89.7	91.6
Ventilation with mask, % [b]	100	68.0	76.8	76.2	76.0	75.8
Intubation, %	62.5	80.2	86.6	78.5	69.8	76.8
Adrenaline, %	0	7.1	7.9	6.1	5.2	6.2
Cardiac massage, %	12.5	8.1	10.6	8.2	6.9	8.2
Advanced CPR, % [c,*]	62.5	80.2	86.6	78.7	70.1	77.0
Surfactant in delivery room, n (%) [a]	n = 7; 1 (14.3)	n = 188; 32 (17.0)	n = 659; 147 (22.3)	n = 988; 191 (19.3)	n = 1,247; 229 (18.4)	n = 3,089; 600 (19.4)
Temperature at admission (°C), mean ± SD (range) [a,d]	n = 4; 34.8 ± 0.4 (34.2-35.0)	n = 96; 34.8 ± 1.1 (31.1-37.8)	n = 380; 35.3 ± 1.1 (32.0-38.6)	n = 537; 35.5 ± 0.9 (32.0-38.0)	n = 732; 35.7 ± 0.8 (31.5-39.0)	n = 1,749; 35.5 ± 0.9 (31.1-39.0)
*Temperature at admission < 36.5°C, N (%)***	4 (100)	91 (94.8)	329 (86.6)	469 (87.3)	608 (83.1)	1,501 (85.8)
CRIB score, median (IQR) [a,*]	n = 6; 10 (8-11.25)	n = 159; 10 (8-13)	n = 574; 8 (6-11)	n = 857; 6 (4-8)	n = 1,098; 4 (2-7)	n = 2,694; 6 (3-9)
Mortality in the first 24 h, n (%) [a,*]	n = 8; 3 (37.5)	n = 199; 69 (34.7)	n = 694; 108 (15.6)	n = 1,029; 95 (9.2)	n = 1,306; 92 (7.0)	n = 3,236; 367 (11.3)

SD: standard deviation; CRIB: Clinical Risk Index for Babies; CPR: cardiopulmonary resuscitation; IQR: interquartile range.

[a] N: total number of patients with available data included in the calculations.

[b] Ventilation with Ambu®, anaesthesia bag, or Neopuff™.

[c] Includes endotracheal intubation, administration of adrenaline, and cardiac massage.

[c] The temperature was not recorded systematically until 2006.

*p < 0.001.

**p = 0.012.

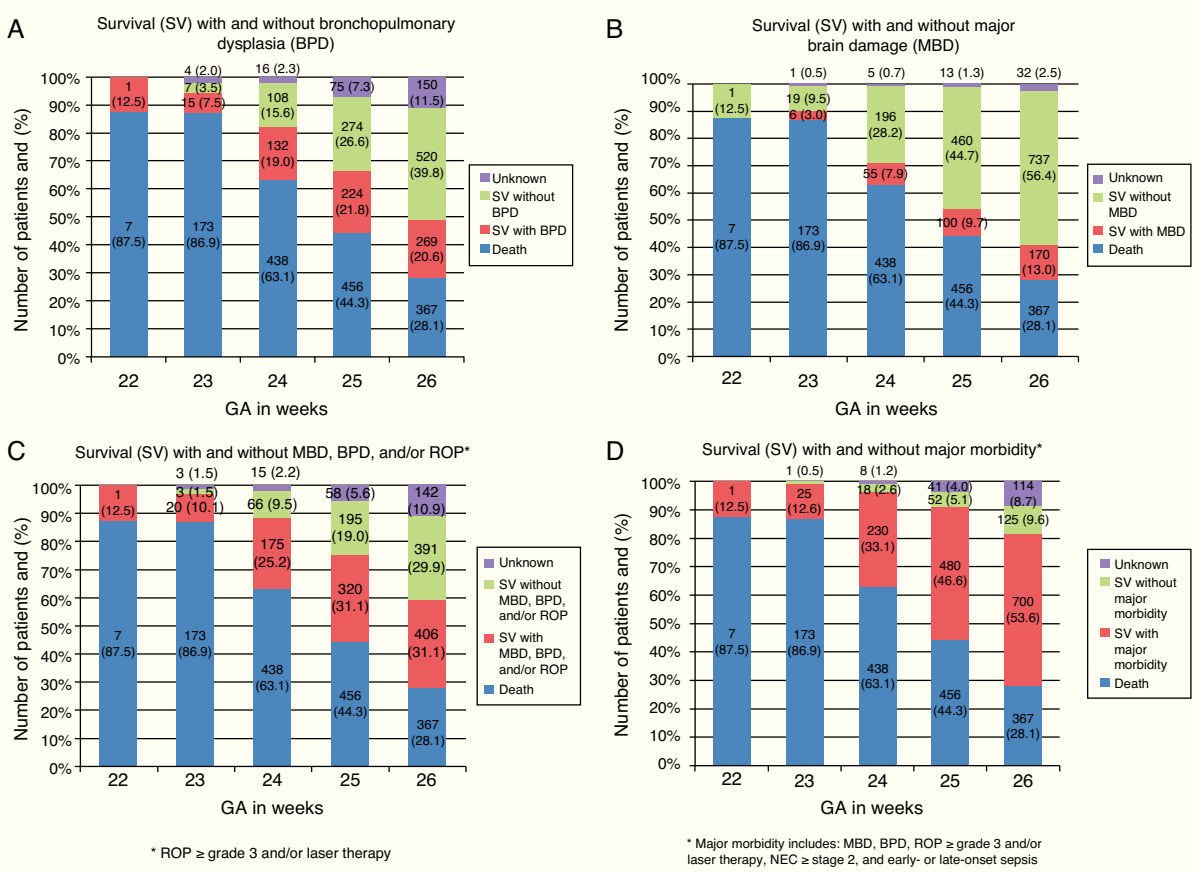

Figure 1 Survival and associated major morbidity.

Other studies have reported a wide variability in the results between different centres and countries, especially in the most inmature infants (22-24 weeks). Usually, the number of infants included in these studies is small, as is the case of single-centre studies, which may contribute to this variability. Another possible reason lies in the choices made by professionals relating to interventions in individual patients. These aspects tend not to be clearly defined in studies, so we cannot analyse to what extent such preferences affect the differences between centres. In our study, we could infer that obstetricians had a more active approach toward patients with higher GA because of the more frequent use of prenatal steroids and the rate of caesarean deliveries as GA increased (Table 1). Most of these children required advanced CPR. However, we noted a more conservative approach of neonatologists toward neonates with 22 weeks GA, as evidenced by the lower frequency of intubation and advanced CPR despite higher rates of neonatal depression in this group of patients, and the greater percentage of such patients who died in the delivery room (Tables 1 and 2).

Most infants included in this study (87.2%) had respiratory distress syndrome (Table 3). In some instances, the diagnosis could not be confirmed because a chest X-ray was not performed in those who died very early on. Furthermore, most of them (86.6%) received surfactant treatment (SF) at some point. Although the benefits of administering SF in infants below 26 weeks GA has been questioned for physiological reasons, in practice it has proven beneficial in this group of patients.[16,17] In recent studies SF was used in 84% (EPICure)[14] and 78% (EPIBEL)[13] of patients, which is a similar frequency to ours.

Administration of SF, either prophylactically or as a rescue therapy, reduces the risk of air leak syndrome and neonatal mortality.[18] In our study, the incidence of pneumothorax was 9.7% (Table 3), and it decreased significantly as GA increased. The incidence of pneumothorax has not been reported systematically in the literature. Nevertheless, our results are very similar to those from the VON data: 12%, 10%, 7.5%, and 6%, at 23, 24, 25, and 26 weeks, respectively[19].

Some of the recently recommended strategies to decrease the incidence of BPD are the avoidance of intubation, a reduction in the use of prophylactic SF administration, and the use of non-invasive respiratory support techniques.[20] The current recommendations is to administer SF once the newborn is stable, except in cases of extremely preterm infants whose mothers did not receive corticosteroids for fetal lung maturation and those who require intubation in the delivery room, in which SF should be administered at that time.[21] In our study it was noteworthy that the overall frequency of intubation during CPR was 76.8% (Table 2), but the frequency of SF administration in the delivery room was only 19.4%. These data diverge strongly with the data of other studies, such as the EPICure2, with intubations in

Table 3 Respiratory morbidity and clinical practice indicators.

GA (admitted alive to the NICU)	22 weeks (N = 8)	23 weeks (N = 199)	24 weeks (N = 694)	25 weeks (N = 1,029)	26 weeks (N = 1,306)	Total (N = 3,236)	p
RDS, n/total (%) [a]	6/7 (85.7)	164/187 (87.7)	599/659 (90.9)	866/986 (87.8)	1,048/1,238 (84.7)	2,683/3,077 (87.2)	0.004
Surfactant at some point, n/total (%) [b]	6/8 (75.0)	175/198 (88.4)	632/692 (91.3)	903/1,028 (87.8)	1,080/1,304 (82.8)	2,796/3,230 (86.6)	< 0.001
PDA, n/total (%)	2/7 (28.6)	90/186 (48.4)	398/645 (61.7)	599/980 (61.1)	708/1,238 (57.2)	1,797/3,056 (58.8)	< 0.001
Surgical closure of PDA, n/total (%)	1/8 (12.5)	27/198 (13.6)	126/691 (18.2)	166/1,021 (16.3)	166/1,299 (12.8)	486/3,217 (15.1)	0.016
Pneumothorax, n/total (%)	2/8 (25.0)	27/195 (13.8)	90/691 (13.0)	111/1,023 (10.9)	81/1,302 (6.2)	311/3,219 (9.7)	< 0.001
Corticosteroids for BPD, n/total (%)	0	14/198 (7.1)	128/692 (18.5)	159/1,017 (15.6)	180/1,295 (13.9)	481/3,210 (15.0)	0.001
Death or oxygen dependency at 28 days, n/total (%)	8/8 (100)	199/199 (100)	669/690 (97.0)	919/1,006 (91.4)	1,011/1,278 (79.1)	2,806/3,181 (88.2)	< 0.001
Survival without oxygen dependency at 36 weeks PMA, n/total (%)	0	7/195 (3.6)	108/678 (15.9)	274/954 (28.7)	520/1,156 (45.0)	909/2,991 (30.4)	< 0.001

PDA: patent ductus arteriosus; BPD: bronchopulmonary dysplasia; PMA: postmenstrual age; RDS: respiratory distress syndrome; NICU: Neonatal Intensive Care Unit.
[a] In every cell, the denominator shows the total number of patients with known data for the variable in question.
[b] Includes administration of surfactant in the delivery room.

Table 4 Survival, length of hospital stay and somatometrics of survivors at home discharge.

GA (admitted alive to NICU)	22 weeks (N = 8)	23 weeks (N = 199)	24 weeks (N = 694)	25 weeks (N = 1,029)	26 weeks (N = 1,306)	Total (N = 3,236)	p
Survived to discharge from hospital, n (%)	1 (12.5)	26 (13.1)	256 (36.9)	573 (55.7)	939 (71.9)	1,796 (55.5)	< 0.001
Age at home discharge (days), mean ± SD (range)	108	123.7 ± 27.5 (87-229)	118.7 ± 29.5 (60-261)	104.4 ± 30.6 (55-285)	89.3 ± 26.3 (40-365)	98.8 ± 30.3 (40-365)	< 0.001
PMA at home discharge (weeks), mean ± SD (range)	38.0	41.3 ± 3.9 (36.3-56.4)	41.4 ± 4.2 (33.1-61.7)	40.3 ± 4.3 (33.4-65.7)	39.1 ± 3.7 (31.7-78.4)	39.9 ± 4.1 (31.7-78.4)	< 0.001
Weight at home discharge (g), mean ± SD (range) [a]	n = 1; 3,300	n = 24; 2,959 ± 605 (1.840-4.350)	n = 236; 2,825 ± 659 (1,885-5,300)	n = 520; 2,696 ± 663 (1,800-7,700)	n = 877; 2,559 ± 579 (1,700-8,770)	n = 1,656; 2,646 ± 626 (1,700-8,770)	< 0.001
Weight gain (g/day), mean ± SD (range)	24.6	18.7 ± 4.6 (10.3-30.2)	18.1 ± 4.0 (8.2-34.3)	18.5 ± 4.2 (5.8-35.9)	19.0 ± 4.1 (8.1-38.8)	18.7 ± 4.1 (5.8-38.8)	0.018
HC at home discharge (cm), mean ± SD (range) [a]	n = 1; 33	n = 21; 33.8 ± 1.9 (30.5-37)	n = 217; 33.9 ± 2.1 (28.5-43)	n = 464; 33.5 ± 2.3 (28.5-45)	n = 777; 33.3 ± 2.0 (26.3-45.5)	n = 1.480; 33.4 ± 2.1 (26.3-45.5)	0.002
Increase in HC (cm/week), mean ± SD (range)	n = 1; 0.8	n = 20; 0.7 ± 0.1 (0.5-0.8)	n = 206; 0.7 ± 0.1 (0.2-1.5)	n = 433; 0.7 ± 0.2 (0.2-1.9)	n = 736; 0.7 ± 0.2 (0.1-2.0)	n = 1,396; 0.7 ± 0.2 (0.1-2.0)	0.143

SD: standard deviation; GA: gestational age; PMA: postmenstrual age; HC: head circumference; NICU: Neonatal Intensive Care Unit.
[a] N: total number of patients with available data included in the calculation of the corresponding parameter.

95% of cases and SF administration in the delivery room in 72%.[22] This finding may be explained by organisational factors or the different protocols of care that exist in the different centres. Despite these differences in initial management, survival without oxygen dependency at 36 weeks postmenstrual age was higher in our setting (30.4% vs. 19.9%), and the use of postnatal steroids for the prevention or treatment of BPD was somewhat lower (15.0% vs. 21%).

The variables most strongly associated with an adverse neurodevelopmental outcome of the patient are severe IVH and cystic periventricular leukomalacia.[23,24] In our study, the incidence of severe IVH in the total of newborns admitted to the NICU was 21.8% (24.3% among those who had an ultrasound done), similar to the incidence found in the EPIBEL study (24.9%).[13] These lesions may have played an important role in mortality, directly or as a result of LDTE, as their incidence in infants who survived was 11.6%. Survival without combined MBD increased progressively with GA (Fig. 1B).

The incidence of ROP in our setting was not high, although its reduction continues to be a key therapeutic objective, as severe ROP has been associated with subsequent visual impairment[25] and functional disability.[26] In the recent study by Farooqi et al.[24], brain damage, BPD, and ROP, alone or in combination, were associated with a poor outcome at 11 years of age. Specifically, 50% of patients with severe ROP had a poor outcome at 11 years of age, compared to a poor outcome in 20% of patients without severe ROP (OR 3.9 [95% CI 1.5-10.1], p = 0.004). After adjusting for morbidity, sex, and GA, brain damage and severe ROP, but not BPD, were still strongly and independently associated with the risk of poor outcome at 11 years.

The incidence of nosocomial sepsis increases as GA decreases, with reported incidences of about 50-60% in infants with GA below 26 weeks.[5] The incidence of late-onset sepsis in our study was 50.5%, and was associated with longer hospital stays among survivors (mean ± standard deviation): 103.8 ± 36 days compared to 85.8 ± 28 days for patients who did not develop it.

The incidence of NEC and FGIP was similar to others reported in the literature. Holman et al. reported NEC incidence rates of 11.5% in infants with weights below 750 g.[27] In the EPIBEL study, the proportion of patients who required surgical intervention for NEC or intestinal perforation was 14.5% among infants admitted to the NICU or 15.9% among survivors, which is slightly higher than the proportion found in our study.[13] Mortality among patients with NEC was higher than among those who did not developed it: 53.5% vs. 43.0% (p < 0.001), which was also the case with those who required surgical intervention (53.9%) versus those who did not (43.9%) (p = 0.002). Furthermore, patients with NEC developed at least one episode of late-onset sepsis more frequently: 19.4% vs. 7.1% (p < 0.001).

The mean hospital stay for our patients was 98.8 ± 30.3 days, and it decreased as GA increased (Table 4), which shows that, along with lower postmenstrual age and lower weight at discharge, infants with higher GA become stable enough to be discharged at an earlier time.

Unlike other population groups, deaths in premature infants occur sooner, as we observed in our study. The causes of death were respiratory (39.4%), infectious (23.8%), neurological (15.8%), other (19%), and unknown (2%). With regard to LDTE, we collected data for 1,204 patients (83.6% of all the deceased), with some form of LDTE recorded for 432 patients (35.9%), which was more frequent among those with lower GA: 42.9% (22 weeks), 51.1% (23 weeks), 39.1% (24 weeks), 33.2% (25 weeks) and 28.8% (26 weeks) (p < 0.001).

In the EPIBEL study, all life support measures were maintained until death in 50% of the patients, some sort of limitation was applied in 39%, and no data were recorded for the remaining 11%.[13] Conversely, in the EPICure study (21-25 weeks), intensive care was actively discontinued in 55.3% of patients.[14]

Our study has some limitations. Although it is the broadest analysis that has been done to date in Spain, we estimate that about one third of the infants in this category may have been left out. Also, we were unable to collect all the data pertaining to morbidity and mortality in some of the infants who were transferred to other centres. However, the missing data was relatively small compared with the size of the population under study.

In conclusion, survival of infants below 23 weeks GA in our setting is very rare. The odds of survival without major morbidity for infants born at 23 and 24 weeks GA are low, and parents should participate in the decision-making process whenever possible and after receiving adequate non-directive guidance. Infants born at ≥ 25 weeks GA have reasonable possibilities of survival, and in the absence of major malformations or other relevant complications they should be offered advanced resuscitation and intensive care. Finnaly, we believe that it is essential to continuously update the data at each centre, and to compare them with the outcomes in the reference population, as shown in this work.

Conflicts of interest

The authors declare having no conflicts of interest.

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