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Survival and Survival without Major Morbidity Seem to Be Consistently Better throughout Gestational Age in 24- to 30-Week Gestational Age Very-Low-Birth-Weight Female Infants Compared to Males

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Abstract
Introduction: Several studies showed advantages in outcomes for very-low-birth-weight (VLBW) female infants. It has been suggested that recent advances in perinatal care might have benefited boys relatively more than girls, making differences disappear. ***Objectives:*** The aims of the study were (1) to determine if sex differences in survival and survival without morbidity in VLBW infants are still present in the context of more advanced perinatal care and (2) to know whether these differences are consistent throughout gestational age (GA). ***Methods:*** Retrospective cohort study in seven countries participating in the Spanish SEN1500 and the South American NEOCOSUR neonatal networks. We included VLBW infants 24–30 weeks' GA, born alive without major congenital anomalies (2013–2016). Major morbidity, survival, and survival without morbidity were compared between male and female infants overall and stratified by GA. ***Results:*** 10,565 patients were included: 5,620 (53.2%) males and 4,945 (46.8%) females. Female infants exhibited a lower incidence rate ratio (95% CI) of respiratory distress syndrome: 0.91 (0.88, 0.94), necrotizing enterocolitis: 0.83 (0.74, 0.93), major brain damage: 0.79 (0.72, 0.86), moderate-severe bronchopulmonary dysplasia (BPD): 0.77 (0.72, 0.83), higher survival: 1.03 (1.01, 1.05), survival without BPD: 1.11 (1.07, 1.16), survival without major brain damage: 1.05 (1.02, 1.08), and survival without major morbidity: 1.14 (1.07, 1.21).

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Survival and survival without morbidity were almost consistently favourable to females throughout GA. ***Conclusions:*** Our findings suggest that perinatal results continue to be favourable for VLBW female infants in the context of current perinatology, and that they are almost consistent throughout GA.

Introduction

During the past decades, we have witnessed technological improvement and changes in perinatal care that have made possible the survival of increasingly more premature newborns around the world, at least in developed countries [1–3]. Similar trends have been observed in recent years in our networks, the Spanish SEN1500 and the South American NEOCOSUR networks [4, 5]. However, despite these global improvements, there are still differences in neonatal mortality depending on the sex of the newborn [6]. Half a century ago, Naeye et al. [7] showed in 2,735 consecutive newborn autopsies that there was a near equal male to female ratio for most disorders in stillborn infants, while disorders arising after birth demonstrated a strong male disadvantage. Nowadays, a body of evidence has shown advantages in morbidity and mortality for very-low-birth-weight (VLBW) female infants. However, it has been suggested that recent advances in perinatal care might have benefited boys relatively more than girls [8], or that differences between sexes might persist in the most immature patients, decreasing with increasing gestational age (GA) or weight [9, 10].

The objective of our work was to determine if differences by sex in morbidity, survival, and survival without major morbidity in VLBW infants ≤30 weeks GA are still present in the context of more advanced perinatal care. We also aimed to determine whether these differences, if present, vary or are consistent throughout GA. We hypothesize that differences in morbidity and mortality between sexes in VLBW infants are no longer present in current practice.

Patients and Methods

We performed a retrospective analysis of data prospectively collected from VLBW infants, 24^0–30^6 weeks GA, from January 2013 to December 2016, in the collaborating centres of the Spanish Neonatal Society (SEN1500) and the South American (NEOCOSUR) networks. Its characteristics and a comparison between them have been published recently [11]. Newborns who died in the delivery room, patients with major congenital anomalies, and those with undetermined sex were excluded. GA was estimated in complete weeks based on the date of the last menstrual period and/or a prenatal ultrasound registered in the maternal record. Management in the delivery room and in the neonatal intensive care unit (NICU) was carried out according to the usual practices in the centres. Demographic, obstetric, and perinatal variables, delivery room and NICU interventions, and outcomes in terms of morbidity and mortality were studied. Mortality was defined as death after admission and before hospital discharge. Major morbidity was considered the presence of major brain damage (MBD), including severe intraventricular haemorrhage (IVH) (grade 3 IVH and/or periventricular haemorrhagic infarction) and/or echogenic or cystic periventricular leukomalacia (PVL); moderate or severe bronchopulmonary dysplasia (BPD), defined as oxygen dependence or invasive or noninvasive respiratory support at 36 weeks postmenstrual age; necrotizing enterocolitis (NEC) ≥ Bell's stage 2; retinopathy of prematurity (ROP) ≥ stage 3 or need for surgical treatment; and/or late-onset neonatal sepsis, defined as suggestive clinical symptoms along with a positive blood culture after 72 h of life.

Table 1. Distribution of patients included by GA and sex

GA (completed weeks)	Males *N* = 5,620	Females *N* = 4,945	Total *N* = 10,565	Proportion by GA, %
24	373	277	650	6.2
25	494	436	930	8.8
26	619	571	1,190	11.3
27	857	726	1,583	15.0
28	1,069	879	1,948	18.4
29	1,084	921	2,005	19.0
30	1,124	1,135	2,259	21.4

Statistical Analysis

Continuous variables are expressed as mean or median and 95% confidence interval (95% CI). Qualitative variables are expressed as proportions and 95% CI. To minimize potential bias, we analysed causal diagrams by means of directed acyclic graphs or causal Bayesian networks [12]. The sex of the infant was the exposure variable and the compound "morbidity and/or mortality" was the outcome variable. Different variables were tested as potential confounding factors or intermediate variables. For the study of the total effect of the exposure on outcomes, true confounders, that is, factors whose modification makes both the exposure and the result vary, were not considered possible [13]. However, for the study of the possible direct effect of sex on outcomes, several intermediate variables were found for which it was necessary to adjust (figures and codes in online suppl. Appendix 1; for all online suppl. material, see www.karger.com/doi/10.1159/000525589). The total and direct effects of the infant's sex on the outcomes of interest were studied by means of Poisson regression. To know the direct effect of sex, we adjusted for GA, birth weight, SGA, and multiple gestation, according to the directed acyclic graphs analysis results. In both cases, robust estimation of the variance and the natural log of the length of stay as an offset variable were used. Outcomes are

Table 2. Patients' characteristics, perinatal interventions, and condition at birth

Variables	Males *N* = 5,620 (53.2%)	Females *N* = 4,945 (46.8%)	*p* value
GA, weeks	27.7 (27.6, 27.7)	27.8 (27.7, 27.8)	0.014
Birth weight, g	1,041.2 (1,034.5, 1,047.8)	1,002.7 (995.4, 1,009.9)	<0.001
Small for GA	11.8 (11.0, 12.6)	11.1 (10.2, 12.0)	0.263
Head circumference, cm	25.6 (25.5, 25.7)	25.2 (25.2, 25.3)	0.002
Multiples	27.9 (26.7, 29.1)	28.3 (27.0, 29.5)	0.654
Assisted reproductive technologies[a]	20.7 (19.2, 22.1)	21.7 (20.2, 23.3)	0.323
Prenatal care (at least one visit)	84.9 (84.0, 85.9)	84.8 (83.8, 85.8)	0.877
Maternal hypertension	19.1 (18.1, 20.1)	23.1 (21.9, 24.3)	<0.001
Chorioamnionitis	22.0 (20.9, 23.2)	22.4 (21.2, 23.6)	0.666
Perinatal interventions and findings			
Antenatal steroids (at least one dose)	88.0 (87.1, 88.8)	89.8 (89.0, 90.6)	0.003
Antenatal steroids (full course)	71.9 (70.6, 73.1)	74.0 (72.7, 75.2)	0.020
Premature rupture of membranes	36.3 (35.0, 37.6)	35.1 (33.7, 36.5)	0.121
Latency from rupture of membranes to birth,[b] days	2.9 (2.7, 3.2)	2.6 (2.4, 2.9)	0.335
Intrapartum maternal antibiotics	51.3 (50.0, 52.6)	49.6 (48.1, 51.0)	0.081
Caesarean section	68.7 (67.5, 69.9)	70.8 (69.5, 72.1)	0.017
Postnatal interventions and findings in delivery room			
First minute Apgar score ≤3	19.5 (18.5, 20.6)	16.6 (15.5, 17.6)	<0.001
5 min Apgar score ≤6	18.8 (17.7, 19.8)	16.8 (15.8, 17.8)	0.009
Oxygen in delivery room	61.7 (60.4, 62.9)	61.9 (60.5, 63.2)	0.843
Bag and mask in delivery room	70.0 (68.8, 71.2)	69.6 (68.4, 70.9)	0.696
Intubation in delivery room	46.5 (45.2, 47.8)	42.8 (41.4, 44.2)	<0.001
Epinephrine and/or chest compressions	8.2 (7.5, 8.9)	6.8 (6.1, 7.5)	0.006
Advanced neonatal resuscitation[c]	46.8 (45.5, 48.1)	43.2 (41.8, 44.5)	<0.001

All values are mean or proportion (95% CI). [a] Data only available for SEN1500 network. [b] Values computed only for patients with premature rupture of membranes (1,945 males and 1,618 females). [c] Advanced neonatal resuscitation includes intubation, chest compression, and/or epinephrine administration.

expressed as incidence rate ratio (IRR) and adjusted IRR and 95% CI. Due to the variability in the management of newborns and in the results among centres [11], as a sensitivity analysis, we show in online supplementary Table 1 the proportions of survival without major morbidity in the different participating centres. Although important variations can be observed from one centre to another, in most of them, better results are observed in female infants. In addition, to assess the potential influence of unmeasured confounders, we carry out the determination of the E-values for the adjusted IRR and the limit of the CI closest to the null [14]. The E-value has been defined as "the minimum strength of association on the risk ratio scale that an unmeasured confounder would need to have with both the exposure and the outcome, conditional on the measured covariates, to fully explain away a specific exposure-outcome association [15]." Although a "large" E-value is context-dependent, in general, the higher the E-value, the less likely it is that there is an unknown, unmeasured factor that could override our best guess, given the data [16].

SPSS version 25 software (IBM Corp, Armonk, NY, USA) was used for statistical analysis. Missing values for most variables of interest were less than 5% (online suppl. Table 2). However, the missing data for severe ROP in survivors was 7.1%. To account for this, we performed both, a complete-case analysis and a multiple imputation analysis with 50 imputations. This study follows the STROBE and RECORD reporting guidelines (checklist as online suppl. Appendix 2).

The Research Ethics Committees of all the participating centres approved the data collection protocol when they joined their network. The Research Ethics Committee of the principal investigator's centre acted as a reference committee (Code 2021-261-1). Given the retrospective and pseudonymized nature of the data, the investigators and the Research Ethics Committee deemed not necessary to obtain informed consent from the parents or legal representatives of the patients.

Results

During the study period, 11,140 VLBW infants were registered, 6,385 (57.3%) in SEN1500 and 4,755 (42.7%) in NEOCOSUR. Among them, 173 (1.6%) who died in the delivery room, 467 (4.2%) with major congenital anomalies (74 of whom died in the delivery room), and 9 with undetermined sex were excluded. Finally, 10,565 patients were included in the study, 5,620 (53.2%) males and

Table 3. Morbidity and interventions after admission to NICU and survival according to sex

Variables	Males *N* = 5,620 (53.2%)	Females *N* = 4,945 (46.8%)	*p* value
Respiratory distress syndrome	82.8 (81.8, 83.8)	77.0 (75.8, 78.2)	<0.001
Pneumothorax	6.4 (5.8, 7.1)	5.1 (4.5, 5.7)	0.003
Oxygen after admission to NICU	84.4 (83.4, 85.3)	81.3 (80.3, 82.4)	<0.001
Noninvasive ventilatory support (nCPAP. biPAP and/or nIPPV)	78.1 (77.0, 79.2)	80.4 (79.3, 81.5)	0.003
Conventional invasive mechanical ventilation	69.1 (67.9, 70.3)	63.8 (62.4, 65.1)	<0.001
High-frequency ventilation	22.8 (21.7, 23.9)	17.7 (16.7, 18.8)	<0.001
Surfactant (at any time; includes surfactant in delivery room)	69.5 (68.3, 70.7)	62.8 (61.4, 64.1)	<0.001
Steroids for BPD	11.1 (10.3, 11.9)	9.3 (8.4, 10.1)	0.002
Oxygen by 28 days of life	42.5 (41.1, 43.8)	37.5 (36.1, 38.9)	<0.001
Oxygen by 36 weeks PMA	22.0 (20.8, 23.1)	17.2 (16.1, 18.3)	<0.001
Discharge home with oxygen	9.5 (8.6, 10.4)	6.6 (5.8, 7.4)	<0.001
Prophylactic indomethacin	3.0 (2.6, 3.5)	2.6 (2.2, 3.1)	0.199
Patent Ductus Arteriosus (PDA)	44.5 (43.2, 45.8)	44.9 (43.5, 46.3)	0.687
Surgical closure of PDA[a]	9.0 (7.9, 10.1)	10.3 (9.0, 11.5)	0.151
NEC	10.9 (10.1, 11.7)	9.3 (8.5, 10.1)	0.005
Surgery for NEC[a]	43.6 (39.7, 47.6)	41.6 (37.0, 46.1)	0.502
Focal gastrointestinal perforation	4.7 (4.2, 5.3)	3.8 (3.3, 4.4)	0.023
Early-onset neonatal sepsis	5.8 (5.2, 6.4)	5.5 (4.9, 6.1)	0.525
LONS	31.7 (30.5, 33.0)	32.0 (30.7, 33.3)	0.767
Candidemia	3.4 (2.7, 4.1)	3.1 (2.4, 3.8)	0.545
IVH (all grades)[b]	34.3 (33.0, 35.6)	28.0 (26.7, 29.3)	<0.001
Severe IVH[b,c]	13.4 (12.5, 14.4)	9.5 (8.6, 10.3)	<0.001
Cystic or echogenic PVL	9.1 (8.3, 9.8)	7.8 (7.1, 8.6)	0.033
MBD[d]	19.9 (18.8, 21.0)	15.9 (14.8, 17.0)	<0.001
ROP ≥ grade 3[e]	5.0 (4.3, 5.6)	5.5 (4.8, 6.2)	0.268
Anaemia that requires transfusion	62.4 (61.1, 63.7)	58.1 (56.7, 59.5)	<0.001
Survival	79.1 (78.1, 80.2)	83.8 (82.7, 84.8)	<0.001
Survival without BPD	59.2 (57.9, 60.5)	68.0 (66.6, 69.3)	<0.001
Survival without MBD	67.2 (66.0, 68.5)	73.0 (71.7, 74.2)	<0.001
Survival without major morbidity[f]	34.1 (32.8, 35.4)	39.9 (38.5, 41.3)	<0.001

Bivariate analysis. All values are proportion (95% CI). BPD, bronchopulmonary dysplasia; PMA, postmenstrual age; PDA, patent ductus arteriosus; IVH, intraventricular haemorrhage; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity; LON, late-onset neonatal sepsis. [a] Computed only for patients with diagnosis of PDA or NEC, in each case. [b] Computed only for patients with an early cerebral ultrasound scan performed (92.3% of patients: 5,163 males and 4,572 females). [c] Third degree IVH and/or intraparenquimal periventricular infarction. [d] MBD includes severe IVH and/or PVL. [e] Computed only for patients with a fundus eye exam (4,283 males and 3,971 females). [f] Major morbidity includes MBD, BPD, NEC, LONS, and/or severe ROP.

4,945 (46.8%) females. The distribution by sex and GA is shown in Table 1. Table 2 shows the patients' characteristics, perinatal interventions, and condition at birth by sex. GA was significantly lower in males with a mean difference (95% CI) of −0.088 (−0.158 to −0.018) weeks. The mothers of female infants were more frequently hypertensive and received more antenatal steroids and intrapartum magnesium sulphate. Female infants had better Apgar scores and needed less intubation, epinephrine, or chest compression during resuscitation.

Table 3 shows the bivariate analysis regarding morbidity and main interventions during NICU stay, as well as survival and survival without morbidity. Female infants exhibited less respiratory morbidity and they received less surfactant administration and ventilatory support. They also exhibited less NEC, IVH, and anaemia that required transfusion. Survival and survival without morbidity were significantly higher in female infants.

Finally, Tables 4 and 5 show the total and direct effects of infant sex on morbidity, survival, and survival without morbidity, globally (Table 4) and specifically by GA (Table 5). Female infants showed overall advantages in respiratory outcomes that were almost consistent from 26- or 27-week GA onward. They also exhibited less NEC, focal

Table 4. Morbidity according to sex (female vs. male)

Morbidity and survival	IRR	95% CI	aIRR[a]	95% CI	*E*-value for point estimate	*E*-value for the limit of the CI closest to null
Respiratory distress syndrome	0.91	0.88, 0.94	0.93	0.90, 0.96	1.36	1.25
Pneumothorax	0.77	0.66, 0.91	0.75	0.64, 0.89	2	1.5
Oxygen by 28 days of life	0.88	0.84, 0.91	0.85	0.81, 0.88	1.63	1.53
Oxygen by 36 weeks PMA	0.77	0.72, 0.83	0.73	0.68, 0.78	2.08	1.88
Oxygen at home discharge	0.72	0.62, 0.83	0.68	0.59, 0.79	2.3	1.85
NEC	0.83	0.74, 0.93	0.78	0.70, 0.88	1.88	1.53
Focal gastrointestinal perforation	0.78	0.65, 0.94	0.75	0.62, 0.90	2	1.46
IVH (all grades)	0.80	0.75, 0.85	0.81	0.76, 0.86	1.77	1.6
Severe IVH[b]	0.69	0.61, 0.78	0.70	0.62, 0.79	2.21	1.85
Cystic or echogenic PVL	0.86	0.75, 0.97	0.87	0.76, 0.99	1.56	1.11
MBD[c]	0.79	0.72, 0.86	0.79	0.72, 0.87	1.85	1.56
ROP ≥ grade 3	1.13	0.95, 1.36	1.04	0.87, 1.24	1.24	1
Anaemia that requires transfusion	0.91	0.88, 0.94	0.89	0.86, 0.93	1.5	1.36
Survival	1.03	1.01, 1.05	1.06	1.04, 1.08	1.31	1.24
Survival without BPD	1.11	1.07, 1.16	1.16	1.12, 1.20	1.59	1.49
Survival without MBD	1.05	1.02, 1.08	1.09	1.06, 1.11	1.4	1.31
Survival without major morbidity[d]	1.14	1.07, 1.21	1.21	1.14, 1.27	1.71	1.54

IRR and adjusted IRR are shown together with the E-values for point estimate and CI (sensitivity analysis). PMA, postmenstrual age; BPD, bronchopulmonary dysplasia; IRR, incidence rate ratio; aIRR, adjusted incidence rate ratio. [a] IRRs adjusted for GA, birth weight, small for GA, and multiple gestation. [b] Severe IVH includes grade 3 IVH and/or periventricular infarction. [c] MBD includes severe IVH and/or PVL. [d] Major morbidity includes MBD, BPD, NEC, late-onset neonatal sepsis, and/or severe ROP.

gastrointestinal perforation, brain damage, and blood transfusion requirements, but not consistently by GA (online suppl. Table 3). Survival and the combined outcomes of survival without BPD, survival without MBD, and survival without major morbidity were significantly higher for girls, and these advantages were almost consistent for all GA from 25 weeks onward (Table 5). The main cause of death was respiratory in both sexes, although it was proportionally more frequent in females than in males (45.7% vs. 37.2%). Other causes of death, such as sepsis (26.0% vs. 24.0%) and brain damage (19.0% vs. 12.1%), were relatively more frequent in boys. The length of stay was slightly shorter for surviving females, but without significant differences by GA. There were also no differences in age at death (online suppl. Table 4).

Discussion

Our results show that advantages in clinical outcomes for female infants persist in the current era of more advanced perinatal care. Female infants exhibited lower mortality and lower respiratory, gastrointestinal, and neurological morbidity, as well as a lower need for blood transfusions during their hospital stay compared to boys. Although the specific analysis by GA shows a similar trend in favour of girls, we only found significant differences for respiratory morbidity, mainly among the most mature patients, after 26- or 27-week GA. It is likely that the smaller number of patients included in the younger GAs had influenced the results, as only 15% of the patients included were born before 26 weeks of gestation. Likewise, survival and the combined outcomes of survival without BPD, survival without MBD, and survival without major morbidity, showed nearly consistent advantages for females from 25 weeks' gestation onward.

Several recent studies have shown a downward trend in morbidity and mortality in very preterm infants [17, 18]. Although the reduction in mortality seems to have been proportionally greater in males, the reported rates continue to show better results in females. As mentioned above, many other studies found similar results, but GA-specific or GA-grouped analyses are scarce [17]. Unlike other studies that suggested that as GA increases, the differences might disappear [8–10], our results show that female advantages with respect to respiratory morbidity and the combined outcomes of survival or morbidity-free survival are nearly constant at all GAs.

Some research has tried to elucidate the biological reasons underlying these advantages of the female sex. Al-

Table 5. Morbidity according to sex (female vs. male), specific by GA (completed weeks)

Morbidity and survival (total and by GA)	RR	95% CI	aRR[a]	95% CI	*E*-value for point estimate	*E*-value for the limit of the CI closest to null
Respiratory distress syndrome	**0.91**	**0.88, 0.94**	**0.93**	**0.90, 0.96**	**1.36**	**1.25**
24	0.68	0.49, 0.95	0.68	0.49, 0.95	2.3	1.29
25	0.76	0.61, 0.94	0.72	0.57, 0.89	2.12	1.5
26	0.86	0.74, 0.99	0.84	0.72, 0.98	1.67	1.16
27	0.90	0.84, 0.96	0.90	0.84, 0.96	1.46	1.25
28	0.91	0.85, 0.96	0.93	0.88, 0.99	1.36	1.11
29	0.92	0.86, 0.98	0.95	0.89, 1.01	1.29	1
30	0.93	0.87, 1.00	0.94	0.87, 1.01	1.32	1
Oxygen by 36 weeks PMA	**0.77**	**0.72, 0.83**	**0.73**	**0.68, 0.78**	**2.08**	**1.88**
24	0.96	0.77, 1.20	0.93	0.74, 1.17	1.36	1
25	0.89	0.76, 1.04	0.86	0.73, 1.01	1.6	1
26	0.80	0.69, 0.94	0.78	0.66, 0.91	1.88	1.43
27	0.83	0.71, 0.97	0.78	0.66, 0.91	1.88	1.43
28	0.69	0.58, 0.83	0.66	0.55, 0.79	2.4	1.85
29	0.72	0.57, 0.91	0.66	0.53, 0.84	2.4	1.67
30	0.60	0.46, 0.79	0.59	0.45, 0.78	2.78	1.88
IVH (all grades)	**0.80**	**0.75, 0.85**	**0.81**	**0.76, 0.86**	**1.77**	**1.6**
24	0.61	0.42, 0.89	0.56	0.40, 0.86	2.97	1.6
25	0.77	0.60, 0.99	0.76	0.59, 0.98	1.96	1.16
26	0.77	0.63, 0.90	0.77	0.62, 0.95	1.92	1.29
27	0.76	0.65, 0.89	0.79	0.67, 0.92	1.85	1.39
28	0.77	0.67, 0.90	0.78	0.67, 0.91	1.88	1.43
29	0.79	0.66, 0.95	0.81	0.67, 0.97	1.77	1.21
30	0.75	0.61, 0.92	0.75	0.61, 0.92	2	1.39
Severe IVH[b]	**0.69**	**0.61, 0.78**	**0.70**	**0.62, 0.79**	**2.21**	**1.85**
24	0.54	0.33, 0.89	0.51	0.31, 0.85	3.33	1.63
25	0.70	0.49, 1.00	0.70	0.49, 1.00	2.21	1
26	0.79	0.61, 1.03	0.80	0.61, 1.06	1.81	1
27	0.53	0.39, 0.72	0.55	0.40, 0.76	3.04	1.96
28	0.67	0.48, 0.92	0.70	0.51, 0.97	2.21	1.21
29	0.78	0.53, 1.19	0.76	0.50, 1.16	1.96	1
30	0.54	0.32, 0.91	0.49	0.29, 0.84	3.5	1.67
Survival	**1.03**	**1.01, 1.05**	**1.06**	**1.04, 1.08**	**1.31**	**1.24**
24	1.05	0.94, 1.19	1.08	0.97, 1.21	1.37	1
25	1.07	1.01, 1.14	1.11	1.05, 1.18	1.46	1.28
26	1.04	0.98, 1.10	1.09	1.03, 1.16	1.4	1.21
27	1.00	0.96, 1.04	1.03	0.99, 1.08	1.21	1
28	1.01	0.97, 1.05	1.04	1.01, 1.08	1.24	1.11
29	1.02	0.98, 1.06	1.06	1.02, 1.10	1.31	1.16
30	1.07	1.03, 1.11	1.07	1.03, 1.12	1.34	1.21
Survival without BPD	**1.11**	**1.07, 1.16**	**1.16**	**1.12, 1.20**	**1.59**	**1.49**
24	1.20	0.81, 1.78	1.34	0.91, 1.98	2.01	1
25	1.24	1.01, 1.52	1.37	1.12, 1.68	2.08	1.49
26	1.25	1.08, 1.45	1.38	1.19, 1.59	2.1	1.67
27	1.08	0.98, 1.19	1.17	1.06, 1.29	1.62	1.31
28	1.11	1.03, 1.20	1.18	1.10, 1.26	1.64	1.43
29	1.06	1.00, 1.13	1.12	1.06, 1.18	1.49	1.31
30	1.12	1.06, 1.18	1.13	1.07, 1.19	1.51	1.34
Survival without MBD[c]	**1.05**	**1.02, 1.08**	**1.09**	**1.06, 1.11**	**1.4**	**1.31**
24	1.07	0.86, 1.34	1.08	0.86, 1.34	1.37	1
25	1.14	1.01, 1.30	1.19	1.04, 1.35	1.67	1.24
26	1.11	1.01, 1.22	1.16	1.05, 1.28	1.59	1.28
27	1.02	0.95, 1.08	1.05	0.98, 1.13	1.28	1
28	1.01	0.95, 1.07	1.05	0.99, 1.12	1.28	1
29	1.02	0.96, 1.07	1.06	1.01, 1.11	1.31	1.11
30	1.10	1.05, 1.15	1.11	1.06, 1.16	1.46	1.31

Table 5 (continued)

Morbidity and survival (total and by GA)	RR	95% CI	aRR[a]	95% CI	*E*-value for point estimate	*E*-value for the limit of the CI closest to null
Survival without major morbidity[d]	**1.14**	**1.07, 1.21**	**1.21**	**1.14, 1.27**	**1.71**	**1.54**
24	1.00	0.34, 2.92	1.44	0.51, 4.10	2.24	1
25	1.02	0.65, 1.60	1.21	0.76, 1.91	1.71	1
26	1.23	0.93, 1.63	1.50	1.14, 1.98	2.37	1.54
27	1.27	0.95, 1.33	1.33	1.13, 1.58	1.99	1.51
28	1.19	1.05, 1.34	1.28	1.14, 1.44	1.88	1.54
29	1.07	0.97, 1.19	1.15	1.04, 1.27	1.57	1.24
30	1.16	1.07, 1.26	1.18	1.08, 1.28	1.64	1.37

IRR and adjusted IRR are shown together with the E-values for point estimate and CI (sensitivity analysis). The values in bold refer to the total number of patients between 24 and 30 weeks' GA. PMA, postmenstrual age; BPD, bronchopulmonary dysplasia. [a] IRRs adjusted for birth weight, small for GA, and multiple gestation, and GA when analysing the whole population (bold figures). [b] Severe IVH includes grade 3 IVH and/or periventricular infarction. [c] MBD includes severe IVH and/or PVL. [d] Major morbidity includes MBD, BPD, NEC, late-onset neonatal sepsis, and/or severe ROP.

though there is no complete agreement, it has been suggested that the male/female ratio at conception is 1:1 and that total mortality during pregnancy is higher for females [19]. It could be speculated that females that survive pregnancy could be better prepared to withstand the stress of childbirth and extrauterine life. In addition, male foetuses have a higher risk of preterm birth and its complications [20]. Special attention has been paid to genetic and endocrine sexual differences, and differences in the inflammatory response and in the response to oxidative or autonomic stress.

The sexual dimorphism seems to be already present in utero. Some studies suggest that the male placenta appears resistant to glucocorticoids since the pathways that normally respond to cortisol, such as cytokine expression, the IGF axis, adrenal function, and growth, are not affected in the presence of a rise in cortisol. In contrast, in female placentas, an increase in cortisol was correlated with changes in cortisol metabolism, cytokine mRNA expression, IGF axis, adrenal function, and growth [21]. In the early stages of gestation, during the canalicular and early saccular stages, the lung development of female foetuses is more advanced, although these differences disappear around 32 weeks of gestation. After birth, girls seem to have better cardiovascular adaptation and better responses to stress. The onset of respiration and exposure to higher oxygen concentrations favour the production of reactive oxygen species. The maturation of the antioxidant systems occurs late in gestation, at the same time as surfactant. However, antioxidant activity in response to antenatal steroids occurs significantly earlier in girls than in boys [22]. Increased activity of antioxidant enzymes in girls decreases reactive oxygen species production, particularly peroxynitrites, favouring pulmonary arterial vasodilation and the fall of resistance. Actually, girls reach target levels of preductal saturation earlier than boys [23]. Years ago, Greenough et al. [24] found, in asphyxiated preterm infants, significantly higher catecholamine levels in girls than in boys and, although not significant, these levels were also higher in non-asphyxiated female babies, which seems to convey a better ability to respond to stress in the female sex. In another study, boys aged 24–28 weeks GA had greater microvascular blood flow during the first 24 h when compared to girls or older boys, which could lead to low systemic flow and hypotension [25], making them need initially more ventilatory and inotropic support [26].

Our study has limitations. This is a retrospective cohort analysis study, in which not all the factors that could potentially influence the results are known and, therefore, they cannot be included in the study. Furthermore, patients who died in the delivery room were excluded, which could modify the overall results in terms of morbidity and mortality. However, this avoids the bias of possible decisions taken before birth based on national policies toward resuscitation at the limit of viability. Online supplementary Table 5 shows the characteristics of patients who died in DR in comparison to those admitted to NICU. On average, they had lower GA and birth weight, and they exhibited congenital anomalies more frequently. On the other hand, the wide geographic coverage could make our results more generalizable, and the relatively short period of time of the study could constitute a strength since it is unlikely that relevant healthcare changes had been intro-

duced during this time that could bias the results. Furthermore, given that some outcomes are competitive with each other, we believe that the combined outcomes of survival without morbidity better reflect the overall quality of care.

In conclusion, in our two big neonatal networks, the Spanish SEN1500 and the South American NEOCOSUR, VLBW female infants, ≤30 weeks GA, had a lower risk of respiratory morbidity, NEC, and brain damage, as well as a higher likelihood of survival and survival without major morbidity. Our data suggests that sex differences in outcomes continue to be favourable for female infants even with more advanced perinatal care. Advantages in respiratory morbidity and in survival, survival without BPD, survival without MBD, or survival without major morbidity seem to be consistent across GA.

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Statement of Ethics

The Research Ethics Committees of all the participating centres approved the data collection protocol when they joined the corresponding network. The Research Ethics Committee of the principal investigator's centre acted as a reference committee (Code 2021-261-1). Given the retrospective and pseudonymized nature of the data, the investigators and the Research Ethics Committee deemed not necessary to obtain informed consent from the parents or legal representatives of the patients.

Conflict of Interest Statement

The authors declare no conflict of interest for the present work.

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Author Contributions

Drs. Vento, Tapia, Fabres, and D'Apremont established the initial agreement collaboration protocol between both networks. Drs. García-Muñoz Rodrigo, Vento, D'Apremont, Fabres, and Tapia conceptualized the study and carried out the standardization of the variables between both networks. Dr. García-Muñoz Rodrigo carried out the statistical analysis and wrote the initial draft. Drs. Zozaya Nieto, San Feliciano, Figueras-Aloy, Saenz de Pipaon, and Genes de Lovera contributed to data collection and literature review. All the authors approved the final version.

Data Availability Statement

Data available on request from the corresponding author.

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