Erratum
April 23, 2021. DOI: 10.1159/000515728

Neonatology

Original Paper

Neonatology 2021;118:289–296
DOI: 10.1159/000513079

Received: June 16, 2020
Accepted: November 16, 2020
Published online: February 25, 2021

Factors Associated with Survival and Survival without Major Morbidity in Very Preterm Infants in Two Neonatal Networks: SEN1500 and NEOCOSUR

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Keywords
Very low-birth weight infant · Morbidity · Mortality · Neonatal networks

Abstract
Introduction: Very low-birth weight (VLBW) infants represent a high-risk population for morbidity and mortality in the neonatal period. Variability in practices and outcomes between centers has been acknowledged. Multicenter benchmarking studies are useful to detect areas of improvement and constitute an interesting research tool. ***Objectives:*** The aim of the study was to determine the perinatal variables and interventions associated with survival and survival without major morbidity in VLBW infants and compare the performance of 2 large networks. ***Methods:*** This is a prospective study analyzing data collected in 2 databases, the Spanish SEN1500 and the South American NEOCOSUR networks, from January 2013 to December 2016. Inborn patients, from 24^0 to 30^6 weeks of gestational age (GA) were included. Hazard ratios for survival and survival without major morbidity until the first hospital discharge or transfer to another facility were studied by using Cox proportional hazards regression. ***Results:*** A total of 10,565 patients, 6,120 (57.9%) from SEN1500 and 4,445 (42.1%) from NEOCOSUR, respectively, were included. In addition to GA, birth weight, small for gestational age (SGA), female sex, and multiple gestation, less invasive resuscitation, and the network of origin were significant independent factors influencing survival (aHR [SEN1500 vs. NEOCOSUR]: 1.20 [95% CI: 1.15–1.26] and survival without major morbidity: 1.34 [95% CI: 1.26–1.43]). Great variability in outcomes between centers was also found within each network. ***Conclusions:*** After adjusting for covariates, GA, birth weight, SGA, female sex, multiple gestation, less invasive resuscitation, and the network of origin showed an independent effect on outcomes. Determining the causes of these differences deserves further study.

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Introduction

Very low-birth weight (VLBW) infants (≤1,500 g), especially if very preterm (<32 weeks of gestational age, GA), constitute a high-risk population for morbidity and mortality in the neonatal period. Moreover, complications that occur during this period are considered the main cause of mortality during early childhood [1–3]. Different studies have highlighted a great variability of results between centers and countries [4–7]. Multicenter and/or benchmarking studies aiming to detect potential areas of improvement are paramount and constitute an important source of epidemiological research data [8].

SEN1500 is a national database created in 2002 [9] in which a variable number of Spanish neonatal units with representation of most administrative regions participate voluntarily. During the study period, 73 units contributed data to the network. The majority of these units are university-associated and are classified as level II or III following the criteria of the Spanish Neonatal Society [10]. SEN1500 is a quasi-population-based network that collects approximately two-thirds of all VLBW infants born in Spain, according to data from the Spanish National Institute of Statistics. On the other hand, NEOCOSUR is a South American multinational neonatal network, created in 1997, including 27 neonatal units from Argentina, Brazil, Chile, Paraguay, Peru, and Uruguay. All participating centers are university-affiliated and represent both public and private tertiary-care institutions (www.NEOCOSUR.org).

The aims of our study were to determine the perinatal variables and interventions associated with survival and survival without major morbidity in VLBW infants and to compare the perinatal management, postnatal interventions, and outcomes between the 2 networks.

Patients and Methods

We analyzed data prospectively collected from January 1, 2013 to December 31, 2016, in the databases from the SEN1500 and NEOCOSUR networks. Both networks collect data from all VLBW infants admitted to the participating units. For the present study, we included inborn patients, from 24^0 to 30^6 weeks of GA. Patients who died in the delivery room and those with major congenital anomalies (see online suppl. Appendix 1; for all online suppl. material, see www.karger.com/doi/10.1159/000513079) were excluded.

GA was estimated according to the date of the last menstrual period, obstetric parameters in an early prenatal ultrasound, and/or the clinical examination after birth. Management in the delivery room and in the neonatal intensive care unit (NICU) was carried out according to the usual practices of the centers. Demographic, healthcare, obstetric, and perinatal variables were studied, as well as delivery room and NICU interventions, and outcomes in terms of morbidity and mortality. Fenton's growth charts were used to classify the newborn according to sex, birth weight, and GA [11].

The main outcomes of the study were survival and survival without major morbidity until discharge from hospital or transfer to another facility. Major morbidity was considered as the presence of severe intraventricular hemorrhage (HIV) (grade 3 and/or periventricular hemorrhagic infarction); echogenic or cystic periventricular leukomalacia; moderate or severe bronchopulmonary dysplasia (BPD), defined as the dependency of oxygen or invasive or noninvasive respiratory support at 36 weeks of postmenstrual age; necrotizing enterocolitis (NEC) ≥ Bell's stage 2; retinopathy of prematurity ≥ grade 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 hours of life.

Statistical Analysis

Before the statistical analyses, all the variables collected by each network and their operational definitions were reviewed. Variables with different names but equal content were renamed by consensus. Some variables were transformed to assure they were measuring the same variable. Continuous variables were expressed as mean and standard deviation and compared using Student's t test. Discrete variables without normal distribution were expressed as median and interquartile range (IQR) and compared using the Mann-Whitney U test. Categorical variables were expressed as proportions n/N (%) and compared by the chi-square or the Fisher exact test, as appropriate. Survival and survival without major morbidity were studied using the Cox proportional hazards regression method. The multivariate model was built including all those factors with potential influence on the results based on the literature review and the group's previous experience. Accordingly, GA, birth weight, small for GA (SGA), sex, multiple gestation, prenatal steroids administration, clinical chorioamnionitis, maternal hypertension, intrapartum antibiotic administration, premature rupture of membranes, caesarean section, Apgar scores at 1 and 5 min of life, less invasive delivery room intervention (defined as the absence of intubation, chest compressions, and/or epinephrine administration), and the network of origin were included in the multivariate regression model as independent variables. Missing values ranged between 0 and 5.6% for all variables of interest. After excluding cases with at least one missing variable, 9,346 (88.5%) and 8,711 (82.5%) patients were retained for survival and survival without major morbidity regression analysis, respectively. All comparisons were conducted two-tailed. A p value <0.05 was considered statistically significant. SPSS version 25 software (IBM Corp, Armonk, NY, USA) was used for statistical analysis.

The Research Ethics Committees of all the participating centers approved the data collection protocol when they joined the corresponding network. Permission for data analysis was obtained from the executive committees of the Spanish SEN1500 and NEOCOSUR networks, following a collaboration agreement.

Results

During the study period, 11,140 inborn VLBW infants between 24^0 and 30^6 weeks of GA were registered in the participating centers, 6,385 (57.3%) in the SEN1500 net-

Table 1. Patient characteristics, perinatal interventions, and condition at birth and after admission to the NICU

Variable	SEN1500 *N* = 6,120 (57.9%) Mean or proportion (95% CI)	NEOCOSUR *N* = 4,445 (42.1%) Mean or proportion (95% CI)
Gestational age, weeks	27.8 (27.8–27.9)	27.6 (27.6–27.7)
Birth weight, g	1,017.6 (1,011.1–1,024.1)	1,030.8 (1,023.3–1,038.3)
SGA, *n* (%)	12.3 (11.5–13.1)	10.4 (9.5–11.3)
Sex (% female)	47.7 (46.4–49.0)	45.6 (44.1–47.1)
Multiples, *n* (%)	32.9 (31.8–34.1)	21.4 (20.2–22.6)
Maternal hypertension, *n* (%)	17.0 (16.0–18.0)	26.1 (24.8–27.4)
Chorioamnionitis, *n* (%)	27.1 (26.0–28.3)	15.9 (14.8–17.0)
Perinatal interventions and findings		
Antenatal steroids, at least one dose, *n* (%)	92.7 (92.0–93.4)	83.4 (82.3–84.5)
Antenatal steroids, complete course, *n* (%)	71.1 (69.9–72.2)	75.9 (74.4–77.3)
Maternal intrapartum antibiotics, *n* (%)	59.4 (58.1–60.7)	39.3 (37.8–40.7)
Caesarean section, *n* (%)	68.2 (67.1–69.4)	71.7 (70.3–73.0)
PROM, *n* (%)	41.4 (40.1–42.7)	28.7 (27.4–30.0)
Time from rupture of membranes to birth (days)[a]	7.2 (6.7–7.4)	8.7 (7.9–9.5)
Postnatal interventions and findings in delivery room		
First min Apgar score ≤3, *n* (%)	15.8 (14.9–16.7)	21.4 (20.2–22.6)
Five-min Apgar score ≤6, *n* (%)	16.7 (15.8–17.7)	19.3 (18.2–20.5)
Bag and mask ventilation, *n* (%)	70.2 (69.0–71.3)	69.3 (67.9–70.7)
Intubation in delivery room, *n* (%)	39.2 (37.9–40.4)	52.5 (51.0–54.0)
Less invasive delivery room intervention, *n* (%)[b]	60.4 (59.1–61.6)	47.4 (45.9–48.8)
Postnatal interventions and findings after admission to NICU		
Any type of oxygen administration during NICU stay, *n* (%)	81.1 (80.1–82.1)	85.5 (84.4–86.5)
Noninvasive ventilatory support, *n* (%)	83.5 (82.6–84.5)	73.2 (71.8–74.5)
Conventional mechanical ventilation, *n* (%)	59.1 (57.9–60.4)	76.9 (75.6–78.1)
Surfactant, any time and indication, *n* (%)	62.1 (60.8–63.3)	72.2 (70.8–73.5)
First dose of surfactant later than 2 h of life, *n* (%)	28.7 (27.1–30.3)	15.5 (14.2–16.8)
Two or more doses of surfactant, *n* (%)[c]	31.6 (30.0–33.2)	46.5 (44.7–48.2)
Total time of invasive mechanical ventilation, days[d]	(*N* = 2,792) 11.6 (10.9–12.4)	(*N* = 2,132) 14.6 (13.8–15.5)
Total time of oxygen administration, days[e]	(*N* = 3,923) 33.5 (32.3–34.7)	(*N* = 2,829) 34.9 (33.6–36.3)

All values are mean or proportion (95% confidence interval). SGA, small for gestational age; NICU, neonatal intensive care unit; PROM, premature rupture of membranes. [a] Values computed only for patients with PROM. [b] Less invasive delivery room intervention denotes the proportion of patients who were not intubated in the delivery room and did not receive chest compressions or epinephrine during initial stabilization. [c] Values computed only for patients who received at least one dose of surfactant. [d] Data calculated on patients who required intubation and survived to hospital discharge. [e] Data calculated on patients who received oxygen after admission to NICU and survived to hospital discharge and do not include patients transferred to other centers or with missing values.

work and 4,755 (42.7%) in NEOCOSUR. In total, 173 newborns (1.6%) died in the delivery room and 467 (4.2%) had major congenital anomalies (74 of whom died in the delivery room). These patients, along with 9 infants with unidentified sex, were excluded. Finally, 10,565 patients were included in the study, 6,120 (57.9%) from SEN1500 and 4,445 (42.1%) from NEOCOSUR.

Table 1 summarizes the general characteristics of patients and perinatal events including interventions in the delivery room and after admission to the NICU. In NEOCOSUR, a higher proportion of mothers received a full cycle of antenatal steroids and delivered by caesarean section. On the other hand, in SEN1500, there was a higher frequency of premature rupture of membranes, maternal

Table 2. Comparison of the incidence of morbidities and survival between the centers of the Spanish Neonatal Network SEN1500 and the Latin American Neonatal Network NEOCOSUR between 2013 and 2016

Variable	SEN1500 (73 centers)	NEOCOSUR (27 centers)
Respiratory distress syndrome	75 (61.3–84.2)	92.3 (84.6–96.4)
Patent ductus arteriosus	39.8 (32.1–47.8)	52.1 (40.9–60.1)
Oxygen by 36 weeks of PMA	17.4 (8.5–25.2)	16.9 (10.7–28.2)
NEC	5.9 (2.5–9.7)	8.9 (6.7–15.0)
Early-onset neonatal sepsis	4.4 (1.6–8.9)	3.8 (1.8–5.7)
LONS	32.1 (25.5–45.5)	22.5 (17.5–28.6)
Severe IVH (grade 3 and/or periventricular hemorrhagic infarction)	9.0 (4.8–12.3)	9.6 (6.5–15.0)
PVL	4.3 (2.3–9.6)	3.7 (1.3–7.1)
Severe ROP (>grade 2)	2.9 (0–5.5)	5.1 (2.4–6.5)
Survival	87.3 (83.3–92.1)	76.7 (70.4–83.5)
Survival without BPD	72.3 (63.5–79.3)	57.6 (54.4–64.5)
Survival without MBD[a]	78.5 (69.4–84.7)	66.2 (61.7–78.7)
Survival without major morbidity[b]	59.6 (46.0–71.5)	44.3 (36.1–54.3)

All values are the median (IQR) for each network of the percentages (%) computed at each individual center. PVL, periventricular leukomalacia; BPD, bronchopulmonary dysplasia; PMA, postmenstrual age; NEC, necrotizing enterocolitis; ROP, retinopathy of prematurity; LONS, late-onset neonatal sepsis; IQR, interquartile range; MBD, major brain damage. [a] MBD, including severe HIV (grade 3 and/or periventricular hemorrhagic infarction), and/or PVL. [b] Major morbidity includes severe intraventricular hemorrhage, PVL, BPD, NEC, ROP > grade 2, and/or LONS.

Table 3. Variables with independent influence in survival and/or survival without major morbidity (univariate and multivariate analysis; Cox regression) in both the Spanish Neonatal Network SEN 1500 and the Latin American Neonatal Network NEOCOSUR taken together

Variable	Survival				Survival without major morbidity			
	crude HR	95% CI	adjusted HR	95% CI	crude HR	95% CI	adjusted HR	95% CI
Gestational age, weeks	1.46	1.44–1.48	1.28	1.25–1.31	1.65	1.62–1.69	1.39	1.34–1.43
Birth weight (for each 100 g)	1.31	1.30–1.32	1.18	1.16–1.20	1.40	1.38–1.42	1.23	1.20–1.26
Small for GA	0.66	0.62–0.71	0.76	0.69–0.84	0.55	0.49–0.60	0.69	0.60–0.79
Sex (female)	1.06	1.01–1.10	1.19	1.13–1.24	1.17	1.11–1.24	1.34	1.26–1.43
Multiples	1.04	0.99–1.09	0.88	0.84–0.93	1.07	1.00–1.13	0.85	0.79–0.91
Antenatal steroids (at least one dose)	1.01	0.93–1.08	1.12	1.03–1.21	1.05	0.94–1.16	1.08	0.97–1.21
Maternal hypertension	1.04	0.99–1.10	1.08	1.01–1.15	1.03	0.96–1.10	1.10	1.01–1.20
PROM	1.06	1.02–1.11	1.02	0.97–1.08	1.12	1.05–1.19	1.09	1.01–1.18
Chorioamnionitis	0.83	0.79–0.88	0.98	0.95–1.02	0.80	0.75–0.86	1.02	0.93–1.11
Maternal intrapartum antibiotics	0.94	0.90–0.99	0.98	0.93–1.04	0.92	0.87–0.97	0.93	0.86–1.00
Caesarean section	1.06	1.01–1.11	0.99	0.94–1.05	1.03	0.97–1.10	1.01	0.94–1.08
One-minute Apgar score	1.17	1.15–1.19	1.02	1.00–1.04	1.20	1.19–1.22	1.05	1.02–1.07
Five-minute Apgar score	1.10	1.09–1.11	1.04	1.01–1.06	1.29	1.26–1.32	1.06	1.02–1.09
Less invasive delivery room intervention	1.88	1.80–1.96	1.15	1.09–1.22	2.51	2.36–2.67	1.23	1.13–1.34
Network of origin (SEN1500 vs. NEOCOSUR)	1.04	0.99–1.08	1.20	1.15–1.26	1.13	1.06–1.19	1.34	1.26–1.43

GA, gestational age; PROM, premature rupture of membranes; HR, hazard ratio.

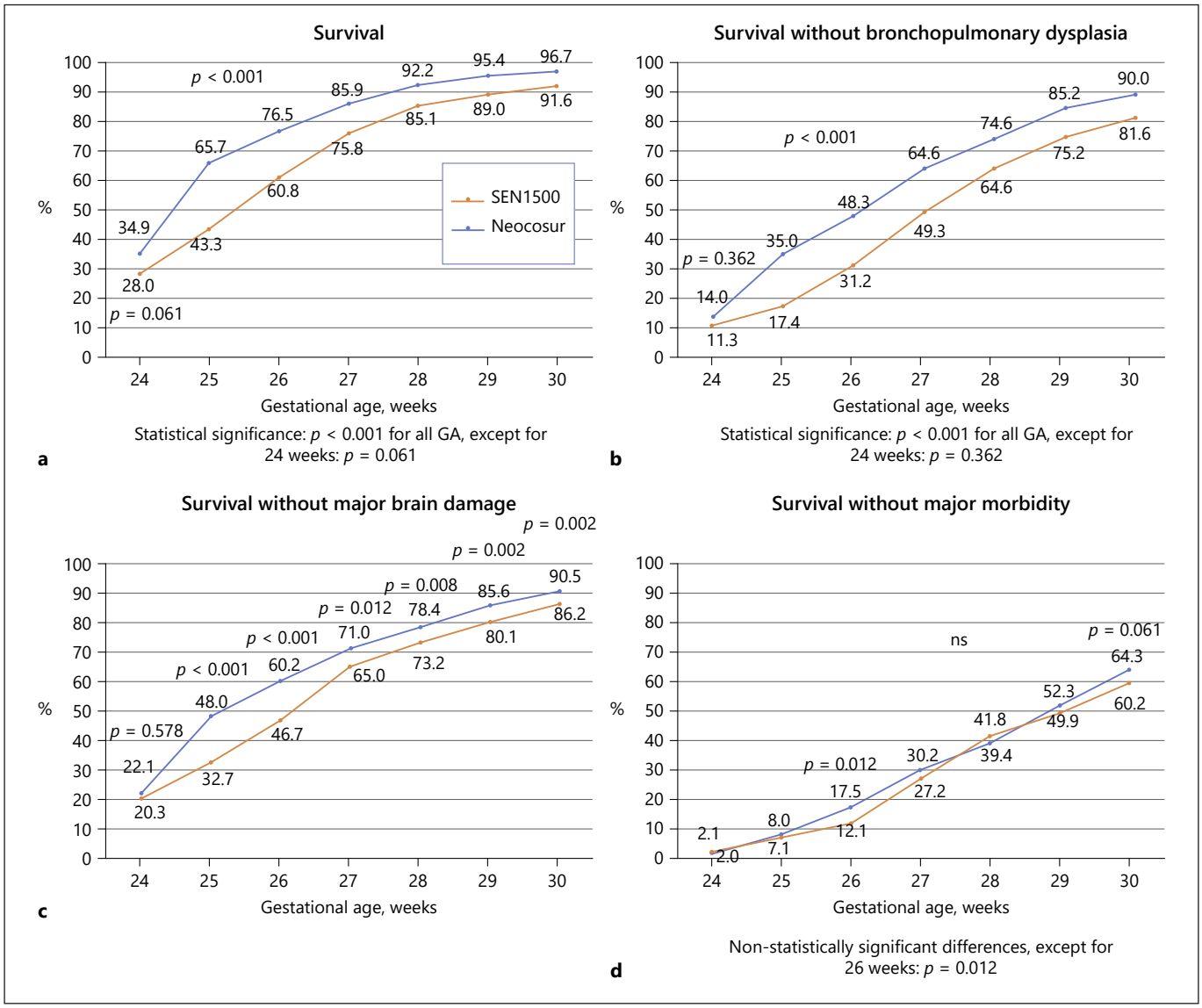

Fig. 1. Comparison of survival (**a**), survival without BPD (**b**), survival without MBD (**c**), and survival without major morbidity (**d**), by completed weeks of gestational age and network (comparisons between groups by the chi-square test). BPD, bronchopulmonary dysplasia; MBD, major brain damage.

chorioamnionitis, and intrapartum administration of antibiotics. Management in the delivery room was more conservative in SEN1500, with a lower intubation rate and, after admission to the NICU, less oxygen administration, less invasive ventilatory support, and a shorter duration of mechanical ventilation.

The number of patients contributed by each center during the study period (4 years) was higher in NEOCOSUR (median [IQR]: 151 [92–232] vs. 66 [38–107]). Morbidity and survival without morbidity were calculated as percentage (%) for each individual center. Then, the median and IQR of these percentages were calculated for each network (Table 2). NEOCOSUR patients exhibited significantly higher cardiorespiratory morbidity and NEC. We found no differences in IVH and retinopathy of prematurity between networks; however, early- and late-onset neonatal sepsis were more frequent in SEN1500. Overall, survival and survival without major morbidity were significantly higher in SEN1500.

Table 3 shows the crude and adjusted hazard ratios for all variables of interest on survival and survival without major morbidity after the Cox regression analysis. Fig-

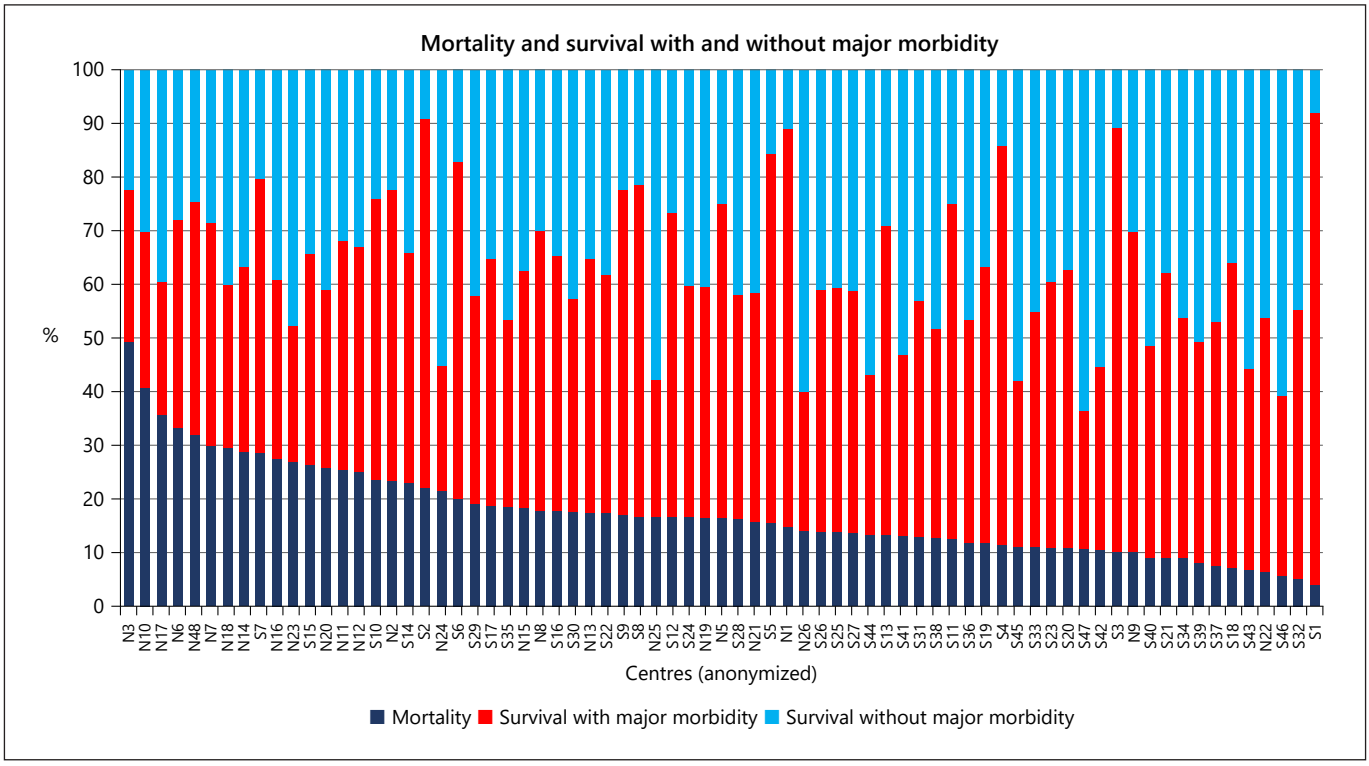

Fig. 2. Individual outcomes among 73 anonymized centers (47 from SEN1500 and 26 from NEOCOSUR) that contributed with >50 patients to the study.

ure 1 shows differences between networks for survival (panel A), survival without BPD (panel B), survival without major brain damage (panel C), and survival without major morbidity (panel D), by weeks of GA. Finally, Figure 2 shows the variability of the main outcomes among 73 anonymized centers (47 from SEN1500 and 26 from NEOCOSUR) that contributed with >50 patients to the study.

Discussion

Our study has evidenced significant demographic differences between both networks. The proportion of SGA patients was higher among SEN1500 neonates but, although overall mortality was higher in this group in comparison to AGA patients (27.7% vs. 17.2%; $p < 0.001$), it was lower in SEN1500 than in NEOCOSUR (21.7% vs. 37.5%; $p < 0.001$). We were unable to differentiate constitutional SGA infants from those with intrauterine growth restriction secondary to a pathological condition that could have implied a potentially worse prognosis. The proportion of multiple gestations was also significantly higher in SEN1500, but mortality among these patients was significantly lower than in NEOCOSUR (12.6% vs. 23.9%; $p < 0.001$). Other significant differences in the bivariate analysis (chorioamnionitis, maternal intrapartum antibiotics, caesarean delivery, etc.) did not show any significant influence on survival and/or survival without major morbidity in the regression model (Table 3).

We also found some relevant differences between the 2 networks in the postnatal care. Intubation and chest compression during initial stabilization were less frequent in SEN1500. Although the proportion of newborns with low Apgar scores at 1 and 5 min was higher in NEOCOSUR (Table 1), we do not have other parameters to compare the relative severity of patients on admission, such as the temperature in the first hour of life [12] or the same risk score, since SEN1500 uses the CRIB score and NEOCOSUR its own risk index [13]. Regarding the Apgar score, it should be also emphasized that it has great interobserver variability, and its usefulness for comparisons has been questioned [14], and new methods of scoring, especially for very preterm infants, have been proposed [15].

Morbidity and rates of survival and survival without major morbidity varied widely between both networks

(Table 2). Interestingly, in a subanalysis including all individual centers that contributed with >50 patients, we found a high variability between centers within each network (Fig. 2). Of note, occasionally, the lower mortality rates were accompanied by a higher rate of survival with major morbidity. Apart from the variables studied, many other factors such as maternal age, parity, socioeconomic status (maternal education and payer for care), late entry into prenatal care, and ethnic, cultural, and organizational differences could explain this variability. In fact, NEOCOSUR has previously reported high variability in outcomes and differences in training of medical and nursing staff between centers [16]. Similarly, significant variability in some aspects of practice and outcomes has been reported by SEN1500 [17].

Regarding the main objectives of our study, we found that GA, birth weight, female sex, and multiple gestation independently increased the likelihood of survival and survival without major morbidity, as has already been noted in previous studies [18]. However, for antenatal steroids [19], the significant effect on survival observed in our study seems to disappear when considering survival without major morbidity (Table 3). Probably some postnatal interventions, such as oxygen administration and invasive mechanical ventilation, together with the development of some morbidities, such as a patent ductus arteriosus, bacterial sepsis, or NEC, could dampen the beneficial effect of steroids on the combined outcome. This is interesting, since we had recently showed that despite an increase in the use of antenatal steroids and a gentler respiratory support during the last decade in Spain, an increase in survival without BPD was only detected among the most immature patients (<27 weeks of GA) [20]. In addition to these factors, the present study shows that providing a less invasive management in the delivery room, with a lower rate of intubations, chest compressions, and/or epinephrine administration, independently increased the probability of survival and survival without major morbidity (Table 3). Gentle management in the delivery room, following the principle of "soft landing," has been promoted in the last decade with great success [21].

Our study has the limitations inherent to cohort analysis studies in which certain factors, which are currently known to influence outcomes, such as delayed umbilical cord clamping, less invasive surfactant administration, exclusive or mixed breastfeeding, and probiotics administration were not systematically collected in the original databases and therefore were not available for analysis. Furthermore, patients who died in delivery rooms were not included in the study. This could modify the global results regarding morbidity and mortality; however, it avoids the bias of possible decisions taken before delivery based on the national policies toward resuscitation at the limit of viability [22, 23]. In fact, in our study, the most marked differences in survival and in survival without major morbidity occurred in patients between 25 and 27 weeks of GA (Fig. 1). This is coincident with reports from other multinational studies in which the highest differences peaked at 24 weeks and decreased with increasing GA [24]. However, the age at death did not vary significantly between networks, occurring at a median (IQR) of 7 (2–17) and 6 (2–15) days in SEN1500 and NEOCOSUR, respectively.

A strength of our study is its broad geographic coverage in a relatively short period of time during which the introduction of new interventions was unlikely, and therefore, no major changes in the routine care of patients would be expected. On the other hand, given that some results are competitive with each other, we believe that the combined result "survival without major morbidity" reflects better the overall quality of care.

In conclusion, our study showed significant differences in some relevant aspects of perinatal management and in the morbidity and mortality of VLBW infants $\leq 30^{6}$ weeks of GA in 2 neonatal networks from Spain and Latin America. Several factors independently influenced the probabilities of survival and survival without major morbidity in our patients. After adjusting for covariates, the network of origin turned out to be an independent predictor for these outcomes. This study will contribute as a starting point for subsequent collaborative studies between both networks in which results will need to be adjusted for this factor. A potential advantage of large multinational collaborative studies is that the time required to detect relevant changes in outcomes as a result of a new intervention is significantly reduced, as has already been highlighted by others [8]. To improve the efficiency of research, it would be essential to standardize the operational definitions of variables and improve the data collection systems and the quality controls of these studies.

Acknowledgements

We are greatly indebted to all the participating hospitals and researchers from the NEOCOSUR Network and the Spanish Neonatal Network SEN1500 (complete list of collaborators as online suppl. Appendix 2). We also like to thank Ms Claudia Musalem for her invaluable assistance in the statistical analysis.

Statement of Ethics

As stated in the main text, the Research Ethics Committees of all the participating centers approved the data collection protocol when they joined the corresponding network. Permission for data analysis was obtained from the executive committees of the Spanish Neonatal Network SEN1500 and NEOCOSUR, following a collaboration agreement between both committees.

Conflict of Interest Statement

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

Author Contributions

Drs. Vento, Tapia, Fabres, D'Apremont, Mariani, and Musante 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, with the assistance of Ms Claudia Musalem, and wrote the initial draft. Drs. San Feliciano and Zozaya Nieto contributed to data collection and literature review. All authors contributed to data collection and literature review, suggested improvements to the manuscript, and approved its late version.

Funding Sources

There was no funding for this research.

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