Original Article

Intellectual outcomes of extremely preterm infants at school age

Running title: Outcomes of extremely preterm infants

Maya Asami, MD; Atsushi Kamei, MD, PhD; Misato Nakakarumai, MA;

Satoko Shirasawa, MD, PhD; Manami Akasaka, MD, PhD;

Nami Araya, MD, PhD; Sachiko Tanifuji, MD; and Shoichi Chida, MD, PhD

Department of Pediatrics, School of Medicine, Iwate Medical University, Japan

Correspondence to: Maya Asami, MD, Department of Pediatrics, School of Medicine, Iwate Medical University, 19-1 Uchimaru, Morioka 020-8505, Japan

Tel: +81-19-651-5111, Fax: +81-19-651-0515

Email: masamill@iwate-med.ac.jp

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Background: The survival rate of extremely preterm (EP) infants (<28 weeks of gestation) has improved dramatically, and there is great interest in the long-term prognosis. The aim of this study was to elucidate the influence of prenatal and postnatal care on long-term intellectual outcome in EP infants.

Methods: Subjects were EP infants admitted to the neonatal intensive care unit from 1982 to 2005. The survival rate and neurodevelopmental outcomes at 6 years of age were analyzed for the periods 1982–1991 (period 1) and 1992–2005 (period 2). Logistic regression analysis was performed to examine risk factors for intellectual impairment.

Results: Survival rate improved significantly from 84.5% (period 1) to 92.4% (period 2; P = 0.007). Follow-up data were obtained from 92 children in period 1 (69.7% of survivors) and from 245 in period 2 (72.3% of survivors). The incidence of intellectual impairment increased from 16.3% (period 1) to 31.0% (period 2). Significant factors associated with intellectual impairment were period 2 (OR, 3.53; P = 0.007), supplemental oxygen at 36 weeks' corrected age (OR, 2.22; P = 0.012), number of days in the hospital (OR, 1.01; P = 0.012), intraventricular hemorrhage (IVH; OR, 3.05; P = 0.024), and later tube-feeding commencement date (OR, 1.10; P = 0.032).

Conclusions: Despite an increase in survival rate, the rate of intellectual impairment increased in period 2. According to risk factor analysis, reducing the incidence of chronic lung disease and/or apnea, IVH, and nutritional deprivation is a key factor in improving the intellectual outcomes of EP infants.

Key words extremely preterm infant, follow-up study, outcome study, risk factor.

Advances in perinatal intensive care have led to improved survival of extremely preterm (EP) infants (<28 weeks of gestation), but EP infants still have a higher incidence of neurodevelopmental impairment compared with term infants.[1] The Iwate Medical University neonatal intensive care unit (NICU) was established in 1982 as the only tertiary center in Iwate Prefecture. Surfactant replacement therapy was conducted in clinical studies for the treatment and prevention of respiratory distress syndrome (RDS) in the NICU before the government approved surfactant as a therapeutic drug in 1987. Surfactant therapy for RDS was associated with reduction in mortality and morbidity related to prematurity in many randomized, controlled studies in developed countries.[2] There is concern, however, that the decreased mortality rate may increase the risk of major neurodevelopmental impairment in RDS infants treated with surfactant. Given that the incidence of RDS is inversely proportional to advancing gestational age, the aim of this study was to clarify neurodevelopmental outcomes at school age of EP infants born between 1982 and 2005 and to elucidate the influence of prenatal and postnatal care on long-term intellectual outcome in the post-surfactant era.

Methods

Subjects

From 1982 to 2005, 542 EP infants were admitted to the NICU, and 488 (90.0%) were discharged alive. We excluded surviving discharged infants with major congenital anomalies at higher risk for poor growth and developmental outcomes.[3] These included

chromosome abnormality (trisomy 21, n = 1), cardiovascular abnormalities requiring surgical repair (n = 3), central nervous system abnormalities (congenital hydrocephalus, n = 2; craniosynostosis, n = 1; Arima syndrome, n = 1), facial and gastrointestinal abnormalities (Goldenhar syndrome, n = 1; cleft lip and palate, n = 2; esophageal atresia, n = 2), genitourinary abnormalities (hypospadias, n = 1), and other anomaly (congenital strangulation ring syndrome, n = 1). We also excluded infants who died after discharge (n = 2). There was no overlapping in the excluded infants. Of the remaining 471 children, 337 (71.5%) were evaluated at a median age of 72 months (range, 67–87 months; IQR, 72–74 months). Of these children, 279 completed the Wechsler Intelligence Scale for Children revised[4] or third edition[5] (WISC-R or WISC-III), and 27 children completed the Tanaka–Binet test.[6] We included 31 severely neurologically impaired children who were not testable with the WISC or Tanaka–Binet test in the statistical analysis (Fig. 1). The survival rate and neurodevelopmental outcomes were assessed for the two separate periods 1982–1991 (period 1) and 1992–2005 (period 2). The study periods were selected based on the following factors: aggressive use of antenatal steroids, additional indication for cesarean section (cesarean section at 23 and 24 weeks of gestation), and earlier use of surfactant for RDS after 1992.[7]

Data collection and terminology

The NICU infant database and follow-up system for discharged infants was set up in 1982, when the NICU was established. Prenatal and postnatal variables are listed in Table 1. We

selected variables that were very likely to affect outcomes or that were reported as risk factors for outcomes in preterm infants. The selected variables were as follows: antenatal steroids to accelerate fetal lung maturity; pregnancy-induced hypertension that involved obstetric or medical intervention; maternal infection with maternal fever, leukocytosis and local pain; gestational age determined from the mother's last menstrual period and confirmed on ultrasonography in the majority of cases; inborn delivery (i.e. infants born in this hospital); small for gestational age (both birthweight and height <10th percentile of the normal values at each gestational age according to published norms for Japanese infants);[8] heavy for gestational age (birthweight >90th percentile of the normal birthweight at each gestational age);[8] RDS diagnosed according to clinical and radiographic criteria and stable microbubble test on amniotic fluid or gastric aspirate obtained at birth;[9,10] complicated RDS with congenital pneumonia/sepsis or circulatory failure; surfactant replacement (Surfacten, Mitsubishi Tanabe Pharma, Osaka, Japan); acquired infection (any infection occurring >5–7 days after birth); symptomatic patent ductus arteriosus (PDA) requiring pharmacological intervention; intraventricular hemorrhage (IVH)[11] grade 2–4; retinopathy of prematurity (ROP) requiring treatment with laser coagulation, cryocoagulation, or both according to the International Committee for Classification of Retinopathy of Prematurity;[12] chronic lung disease (CLD) defined as the use of supplemental oxygen with abnormal chest radiographic features at 36 weeks' corrected age (postmenstrual plus postnatal age); apnea (cessation of breathing >20 s or a shorter respiratory pause associated with oxygen desaturation and/or bradycardia); and tube-feeding establishment date (i.e. when feeding volume reached 100 mL/kg/day).

We did not include the incidence of periventricular leukomalacia because we could not diagnose it using low-resolution brain ultrasound in the 1980s. Magnetic resonance imaging was also not available during this period. Because of lack of information about periventricular leukomalacia which is strongly linked to cerebral palsy,[13] we did not analyze risk factors for cerebral palsy. When the discharged infants reached school age at 6 years, they underwent neurological examination and evaluation with WISC-R or WISC-III or Tanaka–Binet Intelligence Scale. Intellectual impairment was classified as intelligence quotient (IQ) <70. Cerebral palsy was defined as a non-progressive central nervous disorder characterized by abnormal muscle tone and abnormal control of movement and posture, consistent with level 1 or higher in the Gross Motor Function Classification System.[14] Vision impairment was defined as bilateral blindness. Hearing impairment was defined as a hearing aid on one or both sides. Major neurological impairment included one or more of the following problems: intellectual impairment, cerebral palsy, blindness and/or hearing impairment.

Ethics

The present study was implemented under Japanese ethics guidelines concerning epidemiological studies and conducted with the approval of the ethics committee of Iwate Medical University School of Medicine (approval number EH26-4).

Statistical analysis

Statistical analysis for baseline between-group comparisons consisted of chi-squared test or Fisher's exact test for categorical data, and Mann–Whitney U-test for continuous data. The

effect of the specified prenatal and postnatal variables on intellectual impairment was evaluated on stepwise logistic regression analysis. Analysis was performed using IBM SPSS Statistics version 21.0 (IBM, Armonk, NY, USA). Statistical significance was defined as two-sided $P < 0.05$.

Results

Subject characteristics according to study period are listed in Table 1. As expected from the change of management strategy in 1992, the percentages of antenatal steroid use and cesarean section increased from period 1 to period 2. In addition, the percentage of tocolytic agent use, multiple births, maternal infection, inborn delivery, small for gestational age, RDS, surfactant replacement, hypoglycemia, apnea and supplemental oxygen at 28 days after birth significantly increased from period 1 to period 2. The incidence of breech vaginal delivery, heavy for gestational age, ROP, and CLD decreased significantly in period 2 compared with period 1. Gestational age was similar during the two periods, but birthweight was significantly lower in period 2. Both the tube-feeding commencement date and the tube-feeding establishment date were earlier in period 2. The duration of oxygen use and number of days in the hospital increased in period 2.

Table 2 lists survival rate in the NICU and the outcomes of the follow-up survivors at 6 years of age according to study period. The total survival rate significantly improved from 84.5% to 92.4% ($P = 0.007$). The rate of intellectual impairment at 6 years of age was significantly higher in period 2 than in period 1 at 27 weeks of gestation (2.6% vs. 18.1%, $P = 0.032$) and for the whole group (16.3% vs. 31.0%, $P = 0.006$). The rate of cerebral

palsy also increased from period 1 to period 2 for the whole group (6.5% vs. 14.7%, *P* = 0.043). The rates of visual impairment and hearing impairment were similar in both periods. Major neurological impairment increased from period 1 to period 2 at 27 weeks of gestation (5.3% vs. 23.6%, *P* = 0.017) and for the whole group (19.6% vs. 35.9%, *P* = 0.004).

Subject characteristics according to presence of intellectual impairment are listed in Table 3. The group with intellectual impairment had a significantly lower rate of premature rupture of membranes, shorter gestation, lower birthweight, higher rate of RDS, lower 1 min Apgar score, higher rate of IVH, higher rate of necrotizing enterocolitis, higher rate of CLD, higher rate of supplemental oxygen at 36 weeks of corrected age, longer duration of oxygen use, later tube-feeding establishment date, and longer duration of hospital stay than the group without intellectual impairment.

We used logistic regression models to estimate the relationships between intellectual impairment and risk factors. We used all prenatal and postnatal variables listed in Table 1 and the two separate periods as independent variables. Risk factors associated with intellectual impairment were period 2 (OR, 3.53; 95%CI: 1.40–8.87; *P* = 0.007), number of days in the hospital (OR, 1.01; 95%CI: 1.00–1.02; *P* = 0.012), supplemental oxygen at 36 weeks of corrected age (OR, 2.22; 95%CI: 1.19–4.14; *P* = 0.012), IVH (OR, 3.05; 95%CI: 1.16–7.99; *P* = 0.024), and later tube-feeding commencement date (OR, 1.10; 95%CI: 1.01–1.19; *P* = 0.032).

The characteristics of the survivors assessed and those not assessed (i.e. lost to follow up) at 6 years of age are compared in Table 4. The 337 survivors assessed at 6 years of age

had a significantly lower birthweight, higher rate of RDS, higher rate of symptomatic PDA, higher rate of supplemental oxygen at 28 days after birth, later tube-feeding commencement date, later tube-feeding establishment date, and longer duration of hospital stay than the 134 survivors who were not assessed, indicating potentially more severe conditions in the assessed patients compared with the non-assessed patients.

Discussion

We conducted a regional hospital-based cohort study of 542 EP infants born between 1982 and 2005. The survival rate improved in period 2 compared with period 1. Increased survival rates of EP infants during the post-surfactant era have been reported.[15,16] The changes in newborn infant management policies implemented in 1992 in the present NICU seem to be linked to the improved survival rates. When we compared the present survival rates with those in other cohort studies, we found that the present rates were higher. For example, when comparing period 2 with the same period in a multicenter cohort in the USA,[16] the survival rates for infants born at gestational age 24, 25, and 26 weeks during 1993–2007 were 54.9%, 73.8%, and 83.9%, respectively. Similarly, in EP infants born in 2006 in England, the survival rates were 46% at 24 weeks, 68% at 25 weeks, and 78% at 26 weeks of gestation.[15]

Despite an increase in survival rate, the rates of intellectual impairment and cerebral palsy increased in period 2. Similar to the present findings, some studies reported that the rate of neurodevelopmental impairments increased in the 1990s.[17–19] According to logistic regression analysis, period 2, number of days in the hospital, supplemental oxygen at 36

weeks of corrected age, IVH, and later tube-feeding commencement date were significantly associated with an increased risk of intellectual impairment. It is noteworthy, however, that RDS or surfactant replacement was not found to be a risk factor of intellectual impairment in the post-surfactant era.

The increased risk of intellectual impairment in period 2 seemed to be associated with longer hospital stay and longer duration of oxygen use. It is presumed that these variables are indicators of the severity of the neonatal condition. Other possible risk factors are antenatal steroid use, multiple births, maternal infection, lower birthweight, small for gestational age, and apnea. Spinillo *et al*. have suggested that prenatal dexamethasone therapy is associated with an increased risk of adverse neonatal neurologic outcomes.[20] In the present hospital, prenatal dexamethasone was used until the middle of 2003, and it may have been related to intellectual impairment. It is well known that multiple births are the cause of lower birthweight and small for gestational age, and these infants have higher rates of mortality and morbidity related to prematurity.[21,22] The need for supplemental oxygen is associated with not only CLD, but also apnea of prematurity. In previous studies CLD, defined as oxygen dependence at 36 weeks of corrected age, correlated with developmental delay.[19,23] Apnea was also indicated as an adverse prognostic factor. Among EP infants who survived to 36 weeks' postmenstrual age, prolonged hypoxemic episodes (peripheral capillary oxygen saturation <80% for ≥10 s) during the first 2–3 months after birth were associated with adverse outcomes at 18 months' corrected age.[24] Maternal and postnatal infection and inflammation, mechanical ventilation, oxygen toxicity, hypoxia, poor nutrition, and treatment with steroids have been reported to promote lung disease, and all of

these seem likely to affect cognitive development. Radiology of infants at gestational age 23–31 weeks or with extremely low-birthweight (<1000 g) indicates that postnatal dexamethasone for CLD causes an impairment in brain growth, principally affecting the cerebral cortical gray matter.[25,26] In the present study, postnatal dexamethasone was used until the middle of 2003 for infants with severe CLD who needed supplemental oxygen at 40 weeks of corrected age. On logistic regression analysis, however, these variables were not risk factors for intellectual impairment. It is possible that unmeasured or unselected variables could have affected intellectual impairment in period 2.

Intraventricular hemorrhage and later tube-feeding commencement date were also associated with intellectual impairment. IVH causes severe pathological damage to the brain; and Broitman *et al*. provided evidence that it is a major predictor of adverse developmental outcomes.[27] The finding that later tube-feeding commencement date was significantly associated with intellectual impairment was consistent with our previous study of very low-birthweight (<1500 g) infants born during 1982−1991 and who reached adulthood.[28] Stephens *et al*. reported that failure to provide adequate protein and energy intake during the first postnatal week was associated with negative effects on neurocognitive outcome.[29] Currently, many facilities, including the present one, are implementing amino acid-based i.v. nutrition after birth. Delayed tube feeding might have led to postnatal malnutrition and increased the presence of poor intellectual outcomes in the present study.

Kono *et al*. reported that cystic periventricular leukomalacia, gastrointestinal perforation, sepsis, IVH grade 3 or 4, CLD at 36 weeks of corrected age, and treatment for ROP were significantly correlated with death or developmental delay (developmental quotient <70 or delay as judged by physicians) at 3 years of age in a follow-up report of 1826 infants born in 2003 and 2004 with birthweight ≤1500 g.[30] Hoekstra *et al*. reported that normal cranial ultrasound, absence of CLD, female sex, cesarean delivery, and increased birthweight correlated favorably with neurodevelopmental outcome at a mean age of 47.5 months in a follow-up report of 675 infants born at 23–26 weeks' gestation between 1986 and 2000.[31] Neubauer *et al*. reported that high-grade IVH and/or periventricular leukomalacia, neonatal seizures and bowel perforation and/or necrotizing enterocolitis were significant risk factors for developing major neurological impairment at school age in extremely low-birthweight infants born between 1993 and 1998.[32] Although it is difficult to make direct comparisons between other studies and the present one, IVH, CLD, and undernutrition were mostly common risk factors of intellectual impairment. Therefore, the present results support the findings of the previous studies.

Several limitations of this study must be considered when interpreting the results. The follow-up rate was 69.7% in period 1 and 72.3% in period 2, indicating relatively high loss to follow up. We evaluated outcomes in only one NICU and the patients might not be representative of the general population. Given that the gestational age-specific number of EP infants was not available in the present prefecture, we examined the birthweight-specific number of extremely low-birthweight infants. As a result, 55% and 82% of extremely low-birthweight infants registered in Iwate Prefecture of Japan were admitted to

the present NICU in period 1 and period 2, respectively. Therefore, this study might not include infants who did not survive up to NICU admission. This sampling bias may have led to underestimation of the NICU survival rate. This study was started >30 years ago, and neonatal care has changed. In addition, we did not have data on some potential confounders such as periventricular leukomalacia, and socioeconomic factors. Some subjects were difficult to evaluate using the WISC, so the use of this test for cognitive evaluation was also a limitation.

In conclusion, advances and changing policies in perinatal care have led to improved survival rates in EP infants in a hospital-based cohort study. Intellectual impairment, however, increased in period 2 (1992–2005) compared with period 1 (1982–1991). Based on logistic regression analysis, reduction of the incidence of CLD and/or apnea, IVH, and nutritional deprivation seems to be a key factor in improving the intellectual outcomes of EP infants. To achieve long-term survival and improvement of outcomes, further studies are needed to elucidate the cause of neurodevelopmental disorders, including intellectual impairment.

Disclosure

The authors declare no conflict of interest.

Author contributions

A.K. contributed to the conception and design of this study; M.As. performed the statistical analysis and drafted the manuscript; M.N., S.S., and M.Ak. performed neurological

examinations and intelligence tests; N.A. and S.T. collected prenatal and postnatal data; S.C. critically reviewed the manuscript and supervised the whole study process. All authors read and approved the final manuscript.

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Table 1. Characteristics of the study population in period 1 and period 2.

Variables		Period 1 (1982–1991) *n* =92		Period 2 (1992–2005) *n* =245			*p* value
Mother							
	Maternal age at delivery, years, median (range)	30	(18–40)	30	(16–45)		0.517
	Antenatal steroid use	4/92	(4.3)	191/245	(78.0)	<	0.001
	Tocolytic agent use	66/92	(71.7)	208/244	(85.2)		0.007
	Multiple births	8/92	(8.7)	64/245	(26.1)	<	0.001
	Pregnancy-induced hypertension	5/92	(5.4)	30/244	(12.3)		0.073
	Maternal infection	14/91	(15.4)	73/244	(29.9)		0.008
	Cervical incompetency	13/92	(14.1)	27/244	(11.1)		0.453
	Placenta previa	3/92	(3.3)	9/244	(3.7)		1.000
	Placental abruption	2/92	(2.2)	14/244	(5.7)		0.252
	Premature rupture of membranes	24/91	(26.4)	76/245	(31.0)		0.425
	Breech vaginal delivery	15/92	(16.3)	2/245	(0.8)	<	0.001
	Caesarean section	14/92	(15.2)	215/245	(87.8)	<	0.001
Infant							
	Gestational age, weeks, mean (SD)	25.9	(1.1)	25.7	(1.1)		0.102
	Birth weight, g, median (range)	900	(520–1380)	790	(398–1316)	<	0.001
	Gender (male)	47/92	(51.1)	116/245	(47.3)		0.544
	Inborn delivery	72/92	(78.3)	238/245	(97.1)	<	0.001
	Small for gestational age	0/92	(0)	25/245	(10.2)	<	0.001
	Heavy for gestational age	6/92	(6.5)	2/245	(0.8)		0.006
	Tracheal intubation	86/92	(93.5)	238/245	(97.1)		0.199
	RDS	40/92	(43.5)	170/245	(69.4)	<	0.001
	RDS (complicated)	3/92	(3.3)	20/245	(8.2)		0.058
	Surfactant replacement	43/92	(46.7)	191/245	(78.0)	<	0.001
	1-min Apgar score, median (interquartile range)	3	(2–6)	3	(1–5)		0.816
	5-min Apgar score, median (interquartile range)	7	(6–8)	7	(6–7)		0.050
	Hypoglycemia	2/88	(2.3)	33/241	(13.7)		0.002
	Pulmonary air leaks	6/92	(6.5)	6/244	(2.5)		0.097
	Acquired infections	12/92	(13.0)	38/241	(15.8)		0.609
	Symptomatic patent ductus arteriosus	53/92	(57.6)	130/243	(53.5)		0.540
	Ligation of patent ductus arteriosus	19/92	(20.7)	43/242	(17.8)		0.533
	IVH	10/92	(10.9)	17/245	(6.9)		0.262
	Necrotizing enterocolitis	2/92	(2.2)	4/244	(1.6)		0.667
	Retinopathy of prematurity	42/89	(47.2)	44/244	(18.0)	<	0.001
	CLD	44/92	(47.8)	52/242	(21.5)	<	0.001
	Apnea	34/88	(38.6)	197/244	(80.7)	<	0.001
	Oxygen treatment	91/92	(98.9)	245/245	(100.0)		0.273
	Oxygen at 28 days after birth	78/92	(84.8)	238/242	(98.3)		0.001
	Oxygen at 36 weeks of corrected age	37/92	(40.2)	127/242	(52.5)		0.050
	Oxygen at 40 weeks of corrected age	18/92	(19.6)	27/242	(11.2)		0.050
	Duration of oxygen use, days, median (range)	63	(1–168)	70	(0–568)		0.015
	Tube-feeding commencement date, days, median (range)	6	(1–28)	4	(1–25)	<	0.001
	Tube-feeding establishment date, days, median (range)	19	(5–80)	14	(5–65)	<	0.001
	Number of days in the hospital, days, median (range)	123	(48–545)	140	(69–579)		0.003

Data are the number of events/number in group (%) unless otherwise indicated. Denominators vary according to the number of missing data for each variable. CLD, chronic lung disease; IVH, intraventricular hemorrhage; RDS, respiratory distress syndrome; SD, standard deviation.

Table 2. The survival rate in our NICU and the outcomes of the follow-up survivors at 6 years of age in period 1 and period 2 .

	Period	Gestational age (completed weeks)										Total	
		23		24		25		26		27			
NICU survival rate,	Period 1	4/9	(44.4)	15/23	(65.2)	20/23	(87.0)	38/42	(90.5)	59/64	(92.2)	136/161	(84.5)
Number of survivors/	Period 2	13/20	(65.0)	44/51	(86.3)	85/90	(94.4)	98/103	(95.1)	112/117	(95.7)	352/381	(92.4)
number of live births (%)	Total	17/29	(58.6)	59/74	(79.7)	105/113	(92.9)	136/145	(93.8)	171/181	(94.5)	488/542	(90.0)
	p value	0.422		0.059		0.356		0.283		0.328		0.007	
Survivors assessed, *n*	Period 1	2		11		19		22		38		92	
	Period 2	7		36		54		76		72		245	
	Total	9		47		73		98		110		337	
Intellectual impairment, *n* (%)	Period 1	2	(100)	2	(18.2)	4	(21.1)	6	(27.3)	1	(2.6)	15	(16.3)
	Period 2	3	(42.9)	14	(38.9)	20	(37.0)	26	(34.2)	13	(18.1)	76	(31.0)
	Total	5	(55.6)	16	(34.0)	24	(32.9)	32	(32.7)	14	(12.7)	91	(27.0)
	p value	0.444		0.287		0.262		0.614		0.032		0.006	
Cerebral palsy, *n* (%)	Period 1	0	(0)	2	(18.2)	0	(0)	2	(9.1)	2	(5.3)	6	(6.5)
	Period 2	2	(28.6)	3	(8.3)	11	(20.4)	12	(15.8)	8	(11.1)	36	(14.7)
	Total	2	(22.2)	5	(10.6)	11	(15.1)	14	(14.3)	10	(9.1)	42	(12.5)
	p value	1.000		0.578		0.056		0.730		0.489		0.043	
Visual impairment, *n* (%)	Period 1	0	(0)	1	(9.1)	1	(5.3)	0	(0)	0	(0)	2	(2.2)
	Period 2	0	(0)	1	(2.8)	0	(0)	1	(1.3)	0	(0)	2	(0.8)
	Total	0	(0)	2	(4.3)	1	(1.4)	1	(1.0)	0	(0)	4	(1.2)
	p value	−		0.417		0.260		1.000		−		0.301	
Hearing impairment, *n* (%)	Period 1	0	(0)	1	(0.9)	0	(0)	0	(0)	0	(0)	1	(1.1)
	Period 2	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)
	Total	0	(0)	1	(2.1)	0	(0)	0	(0)	0	(0)	1	(0.3)
	p value	−		0.234		−		−		−		0.237	
Major neurological impairments, *n* (%)	Period 1	2	(100)	3	(27.3)	4	(21.1)	7	(31.8)	2	(5.3)	18	(19.6)
	Period 2	4	(57.1)	15	(41.7)	23	(42.6)	29	(38.2)	17	(23.6)	88	(35.9)
	Total	6	(66.7)	18	(38.3)	27	(37.0)	36	(36.7)	19	(17.3)	106	(31.5)
	p value	0.500		0.492		0.108		0.626		0.017		0.004	

NICU, neonatal intensive care unit; −, not determined.

Table 3. Characteristics of the study population with and without intellectual impairment.

Variables		Intellectual impairment *n* =91		No intellectual impairment *n* =246			*p* value
Mother							
	Maternal age at delivery, years, median (range)	29	(16–42)	31	(16–45)		0.291
	Antenatal steroids use	52/91	(57.1)	143/246	(58.1)		0.901
	Tocolytic agent use	65/91	(78.3)	204/246	(82.9)		0.340
	Multiple births	24/91	(26.4)	48/246	(19.5)		0.180
	Pregnancy-induced hypertension	14/91	(15.4)	21/245	(8.6)		0.074
	Maternal infection	24/91	(26.4)	63/244	(25.8)		1.000
	Cervical incompetency	15/90	(16.7)	25/246	(10.2)		0.127
	Placenta previa	2/90	(2.2)	10/246	(4.1)		0.526
	Placental abruption	5/90	(5.6)	11/246	(4.5)		0.773
	Premature rupture of membranes	19/91	(20.9)	81/245	(33.1)		0.032
	Breech vaginal delivery	3/91	(3.3)	14/246	(5.7)		0.575
	Caesarean section	69/91	(75.8)	160/246	(65.0)		0.066
Infant							
	Gestational age, weeks, mean (SD)	25.4	(1.1)	25.9	(1.1)	<	0.001
	Birth weight, g, median (range)	732	(398–1312)	861	(420–1380)	<	0.001
	Gender (male)	44/91	(52.4)	116/246	(47.2)		0.539
	Inborn delivery	84/91	(92.3)	226/246	(91.9)		1.000
	Small for gestational age	10/91	(11.0)	15/246	(6.1)		0.159
	Heavy for gestational age	2/91	(2.2)	6/246	(2.4)		1.000
	Tracheal intubation	90/91	(98.9)	234/246	(95.1)		0.198
	RDS	65/91	(71.4)	145/246	(58.9)		0.011
	RDS (complicated)	10/91	(11.0)	13/246	(5.3)		0.037
	Surfactant replacement	75/91	(82.4)	159/246	(64.6)		0.001
	1-min Apgar score, median (interquartile range)	3	(1–4)	3	(2–6)		0.049
	5-min Apgar score, median (interquartile range)	7	(6–7)	7	(6–8)		0.407
	Hypoglycemia	13/88	(14.8)	22/241	(9.1)		0.159
	Pulmonary air leaks	4/90	(4.4)	8/246	(3.3)		0.740
	Acquired infections	19/87	(21.8)	31/246	(12.6)		0.053
	Symptomatic patent ductus arteriosus	54/90	(60.0)	129/245	(52.7)		0.266
	Ligation of patent ductus arteriosus	17/89	(19.1)	45/245	(18.4)		0.874
	IVH	14/91	(15.4)	13/246	(5.3)		0.005
	Necrotizing enterocolitis	4/90	(4.4)	2/246	(0.8)		0.046
	Retinopathy of prematurity	27/89	(30.3)	59/246	(24.2)		0.261
	CLD	33/90	(36.7)	63/244	(25.8)		0.037
	Apnea	59/89	(66.3)	172/243	(70.8)		0.501
	Oxygen treatment	90/91	(98.9)	246/246	(100.0)		0.270
	Oxygen at 28 days after birth	88/89	(98.9)	228/245	(93.1)		0.051
	Oxygen at 36 weeks of corrected age	63/89	(70.8)	101/245	(41.2)	<	0.001
	Oxygen at 40 weeks of corrected age	16/89	(18.0)	29/245	(11.8)		0.151
	Duration of oxygen use, days, median (range)	81	(4–568)	65	(1–215)	<	0.001
	Tube-feeding commencement date, days, median (range)	4	(2–25)	4	(1–28)		0.091
	Tube-feeding establishment date, days, median (range)	18	(7–65)	14	(5–80)		0.005
	Number of days in the hospital, median (range)	159	(91–579)	130	(48–370)	<	0.001

Data are shown as described in Table 1. CLD, chronic lung disease; IVH, intraventricular hemorrhage; RDS, respiratory distress syndrome; SD, standard deviation.

Table 4. Characteristics of the survivors assessed and those not assessed (lost to follow-up).

Variables		Survivors assessed *n* =337		Survivors not assessed *n* =134		*p* value
Mother						
	Maternal age at delivery, years, median (range)	30	(16–45)	29	(18–42)	0.198
	Antenatal steroids use	195/337	(59.1)	80/134	(59.7)	0.756
	Tocolytic agent use	274/336	(81.5)	102/134	(76.1)	0.202
	Multiple births	72/337	(21.4)	20/134	(14.9)	0.123
	Pregnancy-induced hypertension	35/336	(10.4)	8/134	(6.0)	0.157
	Maternal infection	87/335	(26.0)	43/132	(32.6)	0.169
	Cervical incompetency	40/336	(11.9)	11/134	(8.2)	0.324
	Placenta previa	12/336	(3.6)	2/134	(1.5)	0.368
	Placental abruption	16/336	(4.8)	3/134	(2.2)	0.301
	Premature rupture of membranes	100/336	(29.8)	39/134	(29.1)	0.911
	Breech vaginal delivery	17/337	(5.0)	13/134	(9.7)	0.092
	Caesarean section	229/337	(68.0)	84/134	(62.7)	0.281
Infant						
	Gestational age, weeks, mean (SD)	25.8	(1.1)	25.9	(1.2)	0.178
	Birth weight, g, median (range)	820	(398–1380)	901	(444–1380)	0.033
	Gender (male)	163/337	(48.4)	69/134	(51.5)	0.610
	Inborn delivery	310/337	(92.0)	116/134	(86.6)	0.082
	Small for gestational age	25/337	(7.4)	13/134	(9.7)	0.454
	Heavy for gestational age	8/337	(2.4)	6/134	(4.5)	0.237
	Tracheal intubation	324/337	(96.1)	124/134	(92.5)	0.152
	RDS	212/337	(62.9)	70/134	(52.2)	0.009
	RDS (complicated)	21/337	(6.2)	9/134	(6.7)	0.160
	Surfactant replacement	234/337	(69.4)	80/134	(59.7)	0.051
	1-min Apgar score, median (interquartile range)	3	(1–5)	3	(1–5)	0.533
	5-min Apgar score, median (interquartile range)	7	(6–7)	7	(6–7)	0.343
	Hypoglycemia	35/329	(10.6)	13/130	(10.0)	1.000
	Pulmonary air leaks	12/336	(3.6)	5/134	(3.7)	1.000
	Acquired infections	50/333	(15.0)	19/132	(14.4)	1.000
	Symptomatic patent ductus arteriosus	183/335	(54.6)	57/134	(42.5)	0.019
	Ligation of patent ductus arteriosus	62/334	(18.6)	15/134	(11.2)	0.054
	IVH	27/337	(8.0)	12/134	(9.0)	0.714
	Necrotizing enterocolitis	6/337	(1.8)	2/134	(1.5)	1.000
	Retinopathy of prematurity	86/333	(25.8)	36/132	(22.9)	0.815
	CLD	96/334	(28.7)	42/134	(31.3)	0.326
	Apnea	231/332	(69.6)	99/132	(75.0)	0.258
	Oxygen treatment	336/337	(99.7)	133/134	(99.3)	0.488
	Oxygen at 28 days after birth	316/334	(94.6)	117/133	(88.0)	0.017
	Oxygen at 36 weeks of corrected age	164/334	(49.1)	64/133	(48.1)	0.918
	Oxygen at 40 weeks of corrected age	45/334	(13.5)	20/133	(15.0)	0.659
	Duration of oxygen use, days, median (range)	69	(1–568)	63.5	(0–90)	0.053
	Tube-feeding commencement date, days, median (range)	4	(1–28)	4	(1–19)	0.008
	Tube-feeding establishment date, days, median (range)	15	(5–80)	14	(6–84)	0.029
	Number of days in the hospital, days, median (range)	137	(48–579)	123	(73–671)	0.001

Data are shown as described in Table 1. CLD, chronic lung disease; IVH, intraventricular hemorrhage; RDS, respiratory distress syndrome; SD, standard deviation.

Figure legend

Figure 1. Flow chart of study subjects.

FIQ, full-scale intelligence quotient; IQ, intelligence quotient; NICU, neonatal intensive care unit; WISC, Wechsler intelligence scale for children.