Original Article

Long-Term Neurodevelopmental Outcomes of Premature Infants in Singapore

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Abstract

Introduction: Neonatal care advances have resulted in improved survival but have raised concerns of increase in neurodevelopmental impairment. This study looked at long-term neurodevelopmental outcomes at ages 5 and 8 years of very low birthweight infants born in the 2000s as compared to the 1990s. Neurodevelopmental assessment at 2 years old was compared to that at 5 and 8 years to determine if assessment at 2 years was predictive of later outcomes. Materials and Methods: A retrospective cohort study of consecutive infants with birthweight less than 1250 grams admitted to a tertiary centre in Singapore between January 1994 to December 1995 (Epoch I) and January 2004 to December 2005 (Epoch II) were included. Neurodevelopmental impairment was defined as having an intelligence quotient (IQ) of less than 70, cerebral palsy, legal blindness, or hearing impairment requiring hearing aids. Results: Mean gestational age was lower for Epoch II compared to Epoch I (28.1 ± 2.5 vs 29.4 ± 2.7 weeks, *P* = 0.004). Death or neurodevelopmental impairment rates did not differ (24.3% and 17.1% at 5 years old, *P* = 0.398; 29.1% and 25.0% at 8 years old, *P* = 0.709). There was improvement in visual impairment rate at 8 years in Epoch II (10.7% vs 34.0%, *P* = 0.024). Mean IQ was better in Epoch II (109 and 107 vs 97 and 99 at 5 [*P* = 0.001] and 8 years [*P* = 0.047], respectively). All infants with no neurodevelopmental impairment at 2 years remained without impairment later on. Conclusion: Over a decade, neurodevelopmental outcomes did not worsen despite lower mean gestational age. Long-term improvement in IQ scores and a reduction in visual impairment rates were seen. Our data suggests that children without neurodevelopmental impairment at 2 years are without impairment later on; therefore, they may need only developmental monitoring with targeted assessments instead of routine formal IQ assessments.

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Introduction

The survival rates for very low birthweight (VLBW) infants have increased over the last 2 decades due to advances in neonatal intensive care,[1-7] changes in institutional practices at the turn of the century (including the rise in use of antenatal steroids and decrease in use of postnatal steroids), and the increase in caesarean section deliveries.[8] With improved survival of premature infants, there are concerns about the concomitant increase in neurodevelopmental impairment among survivors. Most studies on neurodevelopmental outcomes of preterm infants focused on short-term outcomes at about 2 years of corrected age.[2-4,6] Recently, there have been studies from Singapore, Japan and Germany that looked at the long-term impacts of these interventions after 5 years of age, showing a general trend in improvement of moderate to severe neurodevelopmental impairment.[9-11] However, long-term neurodevelopmental outcomes in different countries for VLBWs are affected by a wide variety of factors – from the different antenatal, perinatal and neonatal care to

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subsequent follow-up and interventions, social factors such as family setup and parenting practices, and educational factors of schooling such as early intervention programmes and special schools. Hence, it is important to look at the neurodevelopmental outcomes in a particular local setting.

According to the World Health Organization (WHO), Singapore's prematurity rate of 11.5% ranks 67th globally.[12] Low birthweight is the second leading cause of disease burden in children in Singapore, accounting for 7.7% of disability-adjusted life years (DALYs) in 0- to 14-year-old children.[13] Thus, we sought to assess the outcomes in premature infants born during the 2 periods (1994 to 1995 versus 2004 to 2005) that reflected the changes in perinatal practices.

This study aimed to compare the rates of survival, neonatal morbidity, mortality and neurodevelopmental impairment in 2 cohorts of VLBW infants born in our centre in the mid-1990s and mid-2000s, longitudinally at 2, 5 and 8 years of age.

Materials and Methods

This is a retrospective cohort study of consecutive infants with birthweight less than 1250 grams born between January 1994 to December 1995 (Epoch I) and January 2004 to December 2005 (Epoch II).

Although the study was retrospective in nature, the majority of the primary hospitalisation data were collected into the departmental VLBW database prospectively while the infants were still admitted. Surviving infants were assessed at 2 years of corrected age, and 5 and 8 years of chronological age as per the departmental follow-up protocol.

Neurological examinations were performed by a certified neonatologist and standardised assessments were performed by a trained child psychologist. At the corrected age of 2 years, patients underwent the Bayley Scale of Infant Development Edition II (BSID-II) or III (BSID-III), depending on the year it was performed (BSID-III was used for patients born in 2005). The BSID is one of the most widely and commonly used tools to measure developmental delays in high-risk and preterm infants between 1 to 42 months. With the knowledge that BSID-III tends to overestimate ability compared to BSID-II,[14-17] scores of the former were converted using a conversion factor as derived from a study performed on 185 extremely preterm infants that produced a predicted Mental Development Index (MDI) score and a Combined Bayley-III (CBI-III) score, which allowed us to compare scores from BSID-II and BSID-III more accurately.[13] At 5 years of age, patients underwent the Wechsler Preschool and Primary Scale of Intelligence Edition II (WPPSI-II) or III (WPPS-III) depending on the year it was performed. At 8 years of age, they underwent the Wechsler Intelligence Scale for Children Edition III (WISC-III) or IV (WISC-IV) depending on the year it was performed. The WISC is the most commonly used tool for measuring cognitive ability.

Outpatient case notes were retrospectively reviewed and data regarding the child's growth parameters, schooling and interventions received, presence of epilepsy, visual or hearing impairment, neurological examination and results of neurodevelopmental assessments were collected.

Neurodevelopmental impairment at 2 years of age was defined as having BSID-II MDI less than 70 or CBI-III less than 80, cerebral palsy, hearing impairment requiring hearing aids or being legally blind. Neurodevelopmental impairment at 5 and 8 years of age was defined as having full scale intelligence quotient (IQ) score (FSIQ) or performance IQ score (PIQ) (if FSIQ was not available) of less than 70, cerebral palsy, hearing impairment requiring hearing aids or being legally blind. Cases of cerebral palsy were characterised according to the pattern of neurological findings, e.g. diplegia, monoplegia, hemiplegia and quadriplegia, and not according to the severity of impairment.

Intraventricular haemorrhage (IVH) was diagnosed through serial cranial ultrasounds which were performed twice a week for the first 2 weeks of life and subsequently weekly using the Papile et al classification.[18] Necrotising enterocolitis (NEC) was defined according to modified Bell's criteria based on clinical and radiological features.[19] Retinopathy of prematurity (ROP) was diagnosed by paediatric ophthalmologists, which established the presence and staging of ROP according to the international classification of ROP for babies with gestation less than 32 weeks or birthweight less than 1250 grams.[20] Chronic lung disease (CLD) was defined as oxygen dependency at 36 weeks postmenstrual age or beyond. Sepsis (nosocomial) was defined as blood culture-positive sepsis occurring beyond 72 hours of life.

The primary outcomes that were compared for the 2 periods (Epoch I and Epoch II) were death or neurodevelopmental impairment in survivors at 2, 5 and 8 years of age. Secondary outcomes were neurodevelopmental measures at 2, 5 and 8 years of age using scores on standardised neurodevelopmental assessments, cerebral palsy, visual or hearing impairment, and whether the child needed special education. Finally, we analysed for potential factors that may affect neurodevelopmental outcomes. We also assessed whether neurodevelopmental outcomes at 2 years of age predicted the outcomes at subsequent follow-up at 5 and 8 years of age.

The data was analysed using IBM SPSS Statistics 21.0. Categorical variables were analysed using chi-square, parametric data was analysed using independent t-test and non-parametric data was analysed using the Mann-Whitney U test. Logistic regression was used to determine perinatal variables associated with neurodevelopmental impairment.

Spearman's correlation coefficient was used to determine the strength of association between the MDI or CBI score at 2 years of age and the FSIQ or PIQ score at 5 and 8 years of age.

Results

A total of 90 infants in Epoch I and 55 infants in Epoch II were evaluated. The patient disposition is shown in Figure 1.

Of the infants who survived, the baseline characteristics of those who were lost to follow-up were similar to the group who were not, except for higher rates of severe IVH (8.3% vs 1.3%, $P = 0.049$) and major malformations (14.6% vs 3.8%, $P = 0.030$) in the infants lost to follow-up (Table 1).

Table 2 summarises the perinatal characteristics. Infants born in Epoch II had significantly lower gestational age, were more likely to be delivered via caesarean section, had older mothers, were more likely to have maternal gestational diabetes and prolonged rupture of membranes. They were also more likely to have completed at least 1 course of antenatal steroids.

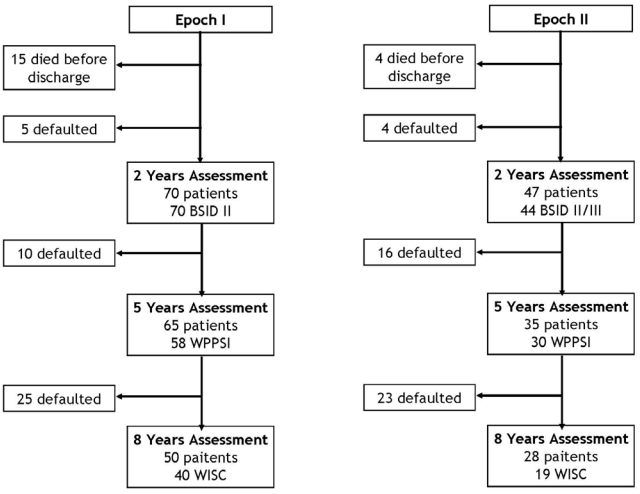

Fig. 1. Flowchart of the recruitment of patients with type 2 diabetes mellitus. BSID: Bayley Scale of Infant Development; WISC: Wechsler Intelligence Scale for Children; WPPSI: Wechsler Preschool and Primary Scale of Intelligence

Table 1. Background Demographics of Survey Participants

	Not Followed-up* n = 48	Followed-up* n = 78	*P* Value
PDA requiring:			
Medical therapy	17 (35.4)	35 (44.9)	0.295
Surgical ligation	1 (2.1)	7 (9.0)	0.123
Chronic lung disease	9 (18.8)	23 (29.5)	0.179
Necrotising enterocolitis	1 (2.1)	3 (3.8)	0.584
ROP	10 (20.8)	21 (26.9)	0.441
Severe ROP†	3 (6.2)	5 (6.4)	0.971
IVH	6 (12.5)	7 (9.0)	0.528
Severe IVH‡	4 (8.3)	1 (1.3)	0.049
Bilateral IVH	4 (8.3)	2 (2.6)	0.140
Shunt for hydrocephalus	1 (2.1)	0 (0.0)	0.201
Seizures requiring anti-convulsants	3 (6.2)	4 (5.1)	0.790
Blood culture-positive septicaemia	7 (14.6)	15 (19.2)	0.505
Meningitis	1 (2.1)	1 (1.3)	0.727
Major malformation	7 (14.6)	3 (3.8)	0.030

IVH: Intraventricular haemorrhage; PDA: Patent ductus arteriosus; ROP: Retinopathy of prematurity

*Numbers represent n (%).

†Severe ROP defined as grade 3 or 4 ROP or ROP requiring laser or cryotherapy.

‡Severe IVH defined as grade 3 or 4 IVH.

Table 2. Perinatal Characteristics

	Epoch I* n = 90	Epoch II* n = 55	*P* Value
Gestational age†	29.4 ± 2.7	28.1 ± 2.5	0.004
Birthweight (grams)‡	1020 (833.8 – 1160.0)	976 (795.0 – 1130.0)	0.360
Small for gestational age	30 (33.3)	16 (29.1)	0.594
Gender (male)	46 (51.1)	27 (49.1)	0.813
Race			0.574
Chinese	63 (70.0)	42 (76.5)	
Malay	18 (20.0)	7 (12.7)	
Indian	5 (5.6)	2 (3.6)	
Others	4 (4.4)	4 (7.3)	
Multiple births	22 (24.4)	14 (25.5)	0.891
Maternal age†	30.8 ± 5.6	32.8 ± 4.2	0.022
Maternal employment	48 (54.5)	36 (63.6)	0.284
Maternal pre-eclampsia	24 (26.7)	16 (29.1)	0.751
Maternal gestational diabetes	1 (1.1)	5 (9.1)	0.019
Antepartum haemorrhage	9 (10.0)	11 (20.0)	0.090
Rupture of membranes >24 hours	17 (18.9)	19 (34.5)	0.034
Antenatal steroids used	45 (50.0)	41 (74.5)	0.004
In-vitro fertilisation	8 (8.9)	7 (12.7)	0.461
Outborn	14 (15.6)	9 (16.4)	0.897
Caesarian delivery	46 (51.1)	39 (70.9)	0.019
1-minute Apgar Score‡	5 (3.0 – 6.3)	6 (5.0 – 7.0)	0.010
5-minutes Apgar Score‡	8 (7.0 – 9.0)	8 (7.0 – 9.0)	0.007

*Numbers represent n (%).

†Mean ± standard deviation.

‡Median (interquartile range).

Table 3 summarises the morbidities and mortality. In terms of the treatment given, infants in Epoch II received continuous positive airway pressure (CPAP) for a significantly longer duration and this is likely due to less proportion of babies being intubated and mechanically ventilated. Infants in Epoch II received significantly lower mean oxygen concentration in the first week of life and postnatal steroids. Rates of major morbidities—defined as IVH, CLD, NEC and ROP—were similar between Epoch I and II. Infants born in Epoch II had a longer length of stay but were discharged at around the same postmenstrual age of 38 to 39 weeks, which may be due to having a lower gestational age at birth.

The mortality rate in Epoch I was higher than Epoch II (16.7% vs 7.3%) but this was not statistically significant. Of the infants who died, 5 in Epoch I had major congenital malformations, including anencephaly, trisomy 18 with oesophageal atresia and hypoplastic left heart syndrome, pentalogy of Cantrell, major chromosomal translocation and hydrops fetalis, and 1 in Epoch II had mesocardia with right lung hypoplasia.

Table 4 summarises the neurodevelopmental outcomes at different ages. There was no statistical difference between the 2 epochs for death or neurodevelopmental impairment as well as neurodevelopmental impairment alone in survivors.

While the MDI at 2 years of age was significantly poorer in Epoch II, IQ scores were significantly better at 5 and 8 years of age. Also, a greater proportion of children in Epoch II had a normal IQ at 5 and 8 years of age, although this was not statistically significant. Using the actual cognitive scores instead of the predicted MDI scores for the patients who had done the BSID-III at 2 years old, the scores of Epoch II approached that of Epoch I (mean MDI score for Epoch I, 91.2 ± 23.0; mean MDI/cognitive score for Epoch II, 87.4 ± 14.2, P = 0.278). Similarly, using the cutoff of MDI or cognitive score of less than 70 to define neurodevelopmental impairment, there was a non-significant trend of improvement in the primary outcome of death or neurodevelopmental impairment at 2 years of age (31.8% for Epoch I vs 22.9% for Epoch II, P = 0.278).

The rate of visual impairment, including myopia and astigmatism, was significantly reduced in Epoch II (8 years of age adjusted OR: 0.13; 95% CI, 0.03 to 0.60). There was no difference in rates of cerebral palsy, hearing impairment, or special school attendance between the 2 epochs.

Logistic regression analysis was conducted to identify predictors of neurodevelopmental impairment at 2, 5 and 8 years of age using the following predictors: demographic and family characteristics including gestational age, birthweight, gender, race, maternal age and employment; neonatal practices including use of antenatal and postnatal steroids, use of surfactant, and mean fraction of inspired oxygen; and morbidities including NEC, ROP, patent ductus arteriosus, CLD and IVH. Birthweight and use of antenatal steroids were significant predictors of neurodevelopmental impairment at 2 years of age (B -0.004, P = 0.001 and B 1.227, P = 0.036 respectively). Presence of CLD was a significant predictor for neurodevelopmental impairment at 5 years of age (B 2.501, P = 0.029). No significant predictors were found for neurodevelopmental impairment at 8 years of age.

Table 3. Major Morbidities and Mortality during Primary Hospitalisation

	Epoch I* n = 90	Epoch II* n = 55	*P* Value
Died	15 (16.7)	4 (7.3)	0.104
Hyaline membrane disease	41 (45.6)	25 (45.5)	0.991
Surfactant given	24 (26.7)	12 (21.8)	0.512
Mechanical ventilation	60 (66.7)	28 (50.9)	0.059
Mechanical ventilation duration (days)§	6 (2 – 23)	7 (2 – 35)	0.880
CPAP duration (days)§	11 (3 – 33)	32 (18 – 43)	0.001
Oxygen exposure			
Duration of oxygen (days)§	7 (1 – 34)	21 (4 – 49)	0.057
Mean oxygen concentration (%)§	30 (22 – 40)	24 (21 – 30)	0.004
Postnatal systemic steroids	17 (18.9)	1 (1.8)	0.002
Chronic lung disease	19 (21.1)	15 (27.3)	0.395
Necrotising enterocolitis	3 (3.3)	3 (5.5)	0.534
ROP	16 (17.8)	15 (27.3)	0.176
Severe ROP†	4 (4.4)	4 (7.3)	0.469
IVH	7 (7.8)	7 (12.7)	0.328
Severe IVH‡	5 (5.6)	2 (3.6)	0.601
Bilateral IVH	4 (4.4)	3 (5.5)	0.783
Shunt for hydrocephalus	0 (0)	1 (1.8)	0.199
Seizures requiring anti-convulsants	6 (6.7)	3 (5.5)	0.769
Blood culture positive septicaemia	13 (14.4)	13 (23.6)	0.162
Meningitis	0 (0)	2 (3.6)	0.069
Length of stay (days)§	60 (53 – 83)	72 (56 – 88)	0.050
Postmenstrual age at discharge (weeks)§	39 (37 – 41)	38 (37 – 40)	0.429

CPAP: Continuous positive airway pressure; IVH: Intraventricular haemorrhage; ROP: Retinopathy of prematurity

*Numbers represent n (%).

†Severe ROP defined as grade 3 or 4 ROP or ROP requiring laser or cryotherapy.

‡Severe IVH defined as grade 3 or 4 IVH.

§Median (interquartile range).

Table 4. Comparison of Primary and Secondary Outcomes

	Age of Follow-up	Epoch I*	Epoch II*	*P* Value
Death or neurodevelopmental impairment	2 years	27/85 (31.8)	16/48 (33.3)	0.853
	5 years	18/74 (24.3)	6/34 (17.1)	0.398
	8 years	16/55 (29.1)	6/23 (25.0)	0.709
Neurodevelopmental impairment	2 years	12/70 (17.1)	12/44 (27.3)	0.197
	5 years	3/58 (5.1)	2/30 (6.5)	0.788
	8 years	1/40 (2.5)	2/19 (10.0)	0.209
MDI at 2 years, FSIQ or PSIQ if FSIQ was not available at 5 and 8 years of age Mean ± SD	2 years	91.2 ± 23.2	79.7 ± 16.3	0.005
	5 years	97.0 ± 12.3	109.0 ± 15.8	0.001
	8 years	99.0 ± 15.0	107.0 ± 12.2	0.047
≤70	2 years	12/70 (17.1)	11/44 (25.0)	0.010
	5 years	1/58 (1.7)	0/30 (0.0)	0.103
	8 years	1/40 (2.5)	0/19 (0.0)	0.740
71 – 84	2 years	10/70 (14.3)	15/44 (34.1)	0.010
	5 years	7/58 (12.1)	0/30 (0.0)	0.103
	8 years	3/40 (7.5)	1/19 (5.3)	0.740
≥85	2 years	48/70 (68.6)	18/44 (40.9)	0.010
	5 years	50/58 (86.2)	30/30 (100.0)	0.103
	8 years	36/40 (90.0)	18/19 (94.7)	0.740
Cerebral palsy	2 years	2/70 (2.9)	3/47 (6.4)	0.355
	5 years	2/64 (3.1)	1/35 (2.9)	0.970
	8 years	0/50 (0.0)	1/28 (3.7)	0.171
Visual impairment (any)	2 years	15/70 (21.4)	2/47 (4.3)	0.010
	5 years	17/64 (26.6)	6/35 (17.1)	0.289
	8 years	17/50 (34.0)	3/28 (10.7)	0.024
Hearing impairment (any)	2 years	2/70 (2.9)	3/47 (6.4)	0.355
	5 years	1/64 (1.5)	2/35 (5.7)	0.243
	8 years	0/50 (0.0)	2/28 (7.1)	0.056
Attending special school	2 years	4/38 (10.5)	3/47 (6.4)	0.103
	5 years	1/65 (1.5)	1/35 (2.9)	0.478
	8 years	2/50 (4.0)	1/28 (3.6)	0.753

FSIQ: Full scale intelligence quotient; MDI: Mental Development Index; PSIQ: Performance scale intelligence quotient; SD: Standard deviation
*Numbers represent n (%).

All the patients who were categorised to have no neurodevelopmental impairment at 2 years of age continued to remain unimpaired at 5 and 8 years of age. Of these children who were unimpaired at 2 years of age, 19.0% had received some form of therapy, including speech therapy, occupational therapy or physiotherapy. Of those who were categorised to have neurodevelopmental impairment at 2 years of age, only about a third of them continued to have impairment at 5 and 8 years of age (Table 5). The positive predictive value of being neurodevelopmentally

Table 5. Neurodevelopmental Impairment at 2, 5 and 8 Years of Age

		Neurodevelopmental Impairment at 5 Years of Age		Neurodevelopmental Impairment at 8 Years of Age	
		Yes	No	Yes	No
Neurodevelopmental impairment at 2 years of age	Yes	5 (33.3)	10 (66.7)	3 (30.0)	7 (70.0)
	No	0 (0.0)	74 (100.0)	0 (0.0)	48 (100.0)

impaired at 8 years of age, if the child was classified as neurodevelopmentally impaired at 2 years of age, was 0.3. The negative predictive value was 1.0. There was a significant, positive correlation between the predicted MDI at 2 years and IQ score at 5 years of age (Spearman correlation coefficient: 0.385, $P \leq 0.001$) and at 8 years of age (Spearman correlation coefficient: 0.312, $P = 0.018$).

Discussion

As expected, there were differences in the 2 epochs studied in our study in terms of perinatal characteristics and morbidities. However, mortality, neurodevelopmental impairment and outcomes were not significantly different between the 2 periods. The overall neurodevelopmental outcomes did not worsen despite a lower mean gestational age in the mid-2000s (Epoch II) compared to the mid-1990s (Epoch I), with an improvement in long-term visual impairment rates and IQ scores. Our data also suggested that children with no neurodevelopmental impairment at 2 years of age were without major impairment at 5 and 8 years of age; therefore, they may need only developmental monitoring for late effects and targeted formal psychological assessments instead of routine repeated cognitive assessments in later years.

Improving survival rates in local VLBW cohorts carry the concern of whether there is a concomitant increase in neurodevelopmental impairment. These improvements in survival and neurodevelopmental outcomes in the mid-2000s in VLBW infants have been well documented in the literature to be associated with increased antenatal corticosteroid use, saturation targeting to reduce excessive oxygen exposure, increased use of surfactant and limiting the use of postnatal systemic steroids.[21,22]

Our study cohort had less patients in Epoch II compared to Epoch I. A 24% reduction in live birth rate in Singapore from the first to the second epoch (74,666 vs 98,189 total live births) may have partially accounted for the difference in admission rates between the 2 epochs.[23] We also expect year-to-year variation in prematurity rates.

The difference between death or neurodevelopmental impairment rates at both 5 and 8 years of age were non-significant for the 2 epochs. However, we should not ignore an important trend towards improved survival rates despite significantly lower gestational age, although this did not reach statistical significance. Looking at the combined outcome of death or neurodevelopmental impairment, there was also a discernible trend towards improvement as the numbers for death or neurodevelopmental impairment were consistently lower at 5 and 8 years of age, although this again did not reach statistical significance. Both of these results could be explained by the small numbers involved.

IQ scores were significantly better in Epoch II with a 12-point increase at 5 years and an 8-point increase at 8 years of age. While we recognise that the Flynn effect (rising intelligence test performance in the general population over time and generations) may be a contributory factor, meta-analyses estimate average IQ score gain per decade to be only 2.8 to 2.93. Although this phenomenon is widely accepted, its substantive meaning and causes remain elusive, varies enigmatically across countries and intelligence domains, and estimates of its magnitude and error of measurement are controversial.[24,25]

The reason behind the observation that the mean adjusted cognitive score on the BSID-III was lower in Epoch 2 is uncertain. However, it is heartening to note that the formal assessments of intellectual ability of these children at 5 and 8 years of age were normal, with the BSID-III at 2 years of age underestimating their intellectual ability. Using the unadjusted BSID-III cognitive scores, patients in Epoch II had a trend towards decreased neurodevelopmental impairment, which was similar to that found at 5 and 8 years of age. The differences in 2 years of age scores and proportion of patients categorised as having neurodevelopmental outcomes between the adjusted and non-adjusted scores for the patients who received the BSID-III were similar to the findings published by the National Institute of Child Health and Network Human Development Neonatal Research in 2012.[17] Whether the BSID-III is an overestimate of cognitive performance or a more valid assessment of emerging cognitive skills than BSID-II is still unclear. In addition, this overestimation of cognitive performance on the BSID-III and the use of the conversion factor have not been validated in our local population.

In our study, all children classified as having no neurodevelopmental impairment at 2 years of age remained classified as having no neurodevelopmental impairment at 5 and 8 years of age (negative predictive value of 1.0). This finding was similar to a study by Hack et al in 2005 which involved 330 extremely low birthweight infants born between 1992 and 1995. This study measured their cognitive functioning at 20 months of corrected age using the BSID-II and at 8 years of age using the Kaufman Assessment Battery for Children, and the negative predictive value was 0.98. This suggested that the assessment at 2 years of age was useful in predicting later outcomes and the information could be used for better counselling of parents and resource allocation (i.e. more resources can be allocated to those who were classified as having neurodevelopmental impairment at 2 years of age). While this may be preliminary data, it suggested that formal IQ assessments may not need to be routinely repeated at later years if the child's IQ was normal earlier on. These children should, however, continue to have developmental surveillance by trained developmental

paediatricians. If the index of suspicion for conditions such as autism, attention-deficit hyperactivity disorder, or learning disorders is high, then targeted formal assessments (beyond cognitive assessments alone) for these conditions should be performed.

The key strength of the study is that the data available has enabled the comparison between the 2 different sets of practices from the 2 periods (Epoch I and II) to see whether the increase in survival of the number of preterm infants over time has correspondingly led to an increase in the neurodevelopmental outcomes in these survivors. This would have been otherwise impossible in a prospective study design since many of the practices and interventions used in the earlier epoch have now become standard of care and it would have been no longer ethically or practically possible to quantify their impact in a real-world, local setting.

Our finding of chronic lung disease being a predictor of neurodevelopmental impairment at 5 years of age is consistent with known literature.[26-28] Interestingly, despite birthweight being a significant predictor of neurodevelopmental outcome at 2 years of age, the neurodevelopmental outcome remained the same in the 2 epochs even though infants in Epoch II had a lower birthweight. This reflects that there were possibly other factors that had an impact on the neurodevelopmental outcomes, for example perinatal practices, which was not statistically significant in our analysis. Unfortunately, owing to the small sample size, we were not able to delve much into the factor(s) that may have contributed to the neurodevelopmental outcomes in these preterm infants. Future studies may explore these factors in a prospective design to understand the role of each of these factors/practices/interventions that may have an impact on the neurodevelopmental outcomes. Alternatively, it may be that, instead of a single intervention/practice, it was a particular set of practices that may have complemented each other resulting in better neurodevelopmental outcomes in these preterm infants.

The limitations of our study were the small sample size and low follow-up rates. Comparison between the group that was followed-up versus that which was not showed that both were similar in baseline characteristics, except for higher rates of severe IVH and major malformations. Given the longitudinal nature of the data analysis, especially for an uncommon disease, increasing the sample size by way of inclusion of patients from various centres may introduce more biases on account of confounding factors such as differences in neonatal care practices and disease severity. At the same time, expanding the period of data may introduce more biases on account of the changes in neonatal practices with time. Having a control group of typically developing children born in Singapore in the same 2 periods and measuring their IQ scores would have helped to confirm if the improvement in IQ score is truly significant.

Conclusion

Overall neurodevelopmental outcomes over a decade did not worsen despite a lower mean gestational age. Long-term improvement in IQ scores and a reduction in visual impairment rates were seen. The assessment of neurodevelopmental impairment at 2 years of age may serve as a good cutoff to predict 5- and 8-year outcomes, thus requiring only developmental monitoring for late effects and targeted formal assessments as needed. However, these are preliminary findings and further studies would be required to understand the reasons underlying the differences in outcomes observed in the 2 periods in order to delineate the possible factors that have contributed to the neurodevelopmental outcomes.

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