


Changes in Mortality and Cerebral Palsy in Extremely Low-Birth-Weight Infants in a Tertiary Center in Hong Kong

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Abstract

Introduction. We retrospectively reviewed a cohort of extremely low-birth-weight (ELBW) babies born at Queen Mary Hospital and explored if there is any time trend in survival and short-term neurodevelopmental outcomes. **Methods.** We included ELBW infants born at Queen Mary Hospital between 2008 and 2015. The relationships between multiple risk factors with survival and neurodevelopmental outcomes were analyzed by either Cox regression or univariate logistic regression analysis. We also compared this birth-year period with our previous study from 1993 to 2002. **Results.** Two hundred seventeen ELBW infants were delivered during the study period. There was significantly higher overall survival rate (81.1%) in 2008 to 2015 compared with 71.4% in 1993 to 2002. One hundred forty-three out of 176 (81%) survivors were assessed at a corrected mean age of 18.1 months. A total of 4.2% had cerebral palsy. There were significantly lower rates of cerebral palsy in 2008 to 2015 (4.2%) compared with 1993 to 2002 (13.5%). **Conclusions.** We showed a temporal improvement in survival and short-term neurodevelopmental outcomes.

Keywords

extremely low-birth-weight, outcomes, Hong Kong

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Introduction

Survival of preterm babies has increased worldwide,¹ with a concomitant decline in severe neonatal morbidity. However, the risk of neurodevelopmental disabilities remains high in children who were born preterm.² Rate of survival with neurodevelopmental impairment increased over time.³ The highest rate of mortality and morbidity had been reported in those infants born weighing <1000 g. Risk factors identified to affect neurodevelopmental outcomes include severe intraventricular hemorrhage, cystic periventricular leukomalacia, and congenital malformation in previous study.^{2,4}

We retrospectively reviewed a cohort of extremely low-birth-weight (ELBW) babies born at a tertiary perinatal center in Hong Kong (Queen Mary Hospital [QMH]) during the period of 2008 to 2015. We explored if there is any time trend in survival, major morbidity, and short-term neurodevelopmental outcomes, and we

identified significant factors that might account for any observable changes.

Methods

Study Population and Data Collection

The study was conducted at QMH, Hong Kong. QMH is a regional hospital with an annual delivery rate of around 3500 to 4500 and is also a tertiary perinatal center that receives referrals requiring complicated perinatal care.

We included infants with birth weight ≤ 1000 g born at QMH between January 1, 2008, and December 31, 2015.

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Infants born outside of QMH were excluded. Data were retrieved from the Clinical Data Analysis and Reporting System (CDARS) under Hospital Authority and Vermont Oxford Network database. University of Hong Kong/Hospital Authority Hong Kong West Cluster Institutional Review Board (IRB) approval was obtained.

Baseline infant and maternal characteristics including birth weight, gestational age (GA), sex, plurality of pregnancy, small for gestational age (SGA; defined as birth weight of <10th percentile for gender and GA), use of antenatal steroid, and Apgar score ≤ 3 at 1 minute of life were recorded. Neonatal medical conditions including use of surfactant for respiratory distress syndrome (RDS), severe intraventricular hemorrhage (IVH; defined as grade 3 or 4 IVH), patent ductus arteriosus requiring ligation, necrotizing enterocolitis (NEC; defined as stage ≥ 2 of Bell's criteria), early-onset sepsis (defined as bacterial pathogen identified from a blood and/or cerebrospinal fluid culture within 72 hours of life), severe retinopathy of prematurity (ROP; defined as stage III or above according to international classification), chronic lung disease (defined as supplemental oxygen use at a postmenstrual age of 36 weeks), and home oxygen dependency were studied. Duration of mechanical ventilation and length of hospital stay among survivors were also included.

Primary outcome was survival on discharge. Secondary outcomes included neurodevelopmental outcomes and growth failure at a corrected age of 18 to 24 months. Neurodevelopmental outcomes were evaluated using the Griffiths Mental Developmental Scales–Extended Revised by pediatric neurologist or developmental pediatrician. Infants were considered to have neurodevelopmental or behavioral problem if they had at least one of the following conditions: cognitive impairment (Griffiths Developmental Quotient [DQ] < 2 standard deviation [SD] overall or at least in one subscale), cerebral palsy, profound visual or hearing impairment, autism spectrum disorder, and attention deficit hyperactivity disorder. Growth failure was defined as growth parameters (body weight, head circumference, and body height) of less than third percentile for gender and age.

Need for special education service referral and presence of epilepsy at the corrected age of 18 to 24 months were also examined.

Interval of neurological/developmental follow-up depends on any abnormality being detected; if assessment is normal at a corrected age of 18 to 24 months, child will be seen again at around 4 to 5 years old.

Statistical Analysis

Demographic data were expressed in mean, median, and percentages when appropriate. Chi-square test was used

for categorical variables and median test for continuous variables. The relationships between multiple risk factors with survival, neurodevelopmental outcomes, and growth failure were analyzed by either Cox regression or univariate logistic regression analysis. If more than one factor is being identified, further analysis using multiple logistic regression will be performed. We also compared the birth-year period (2008-2015) with our previous study from 1993 to 2002.⁵ However, due to unavailability of some of the raw data in the cohort of 1993 to 2002, comparisons using the above-mentioned statistical analysis were not possible in some parameters. All *P* values were 2-tailed, and a *P* value of $< .05$ was considered statistically significant. SPSS 24.0 was used for all statistical analyses.

Ethical Approval and Informed Consent

This study received IRB approval by the IRB of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (Approval #UW 19-376). According to the retrospective nature of the study, the IRB waived the requirement for informed consent.

Results

Demographic Data and Perinatal Characteristics

The perinatal characteristics of the study cohort are shown in Table 1. Two hundred seventeen infants weighing ≤ 1000 g were delivered during the study period of 2008 to 2015. Mean GA was 26.5 ± 2.3 weeks, with a mean birth weight of 762 ± 148 g. One hundred twelve (51.6%) were male infants, 68 (31.3%) were born via multiple pregnancy, and 63 (29%) of them were born SGA. Two hundred (92.2%) infants were given antenatal steroid before birth, and 61 (28.1%) were born with Apgar score ≤ 3 at 1 minute of life.

Comparison Between 1993-2002 and 2008-2015 Birth Cohorts. The proportion of babies born SGA and with Apgar score at 1 minute of life ≤ 3 were significantly lower in the 2008 to 2015 cohort ($P = .01$ and $P = .03$, respectively), while the use of antenatal steroid was significantly higher ($P = .0001$) than in the 1993 to 2002 cohort (Table 1).

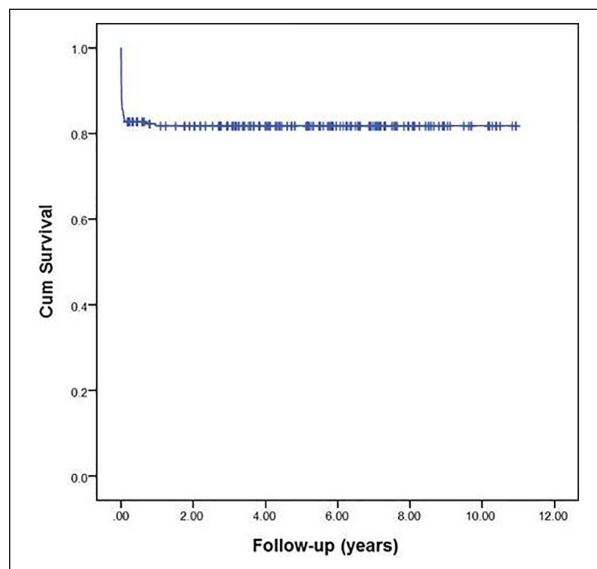
Survival

Figure 1 shows the survival curve for birth years 2008 to 2015, with an overall survival of 81.1% (176/217 infants survived). Table 2 shows the survival rate on discharge. Survival on discharge was highest in the group with a

Table 1. Perinatal Characteristics.

	1993-2002	2008-2015	P
Number of live births	234	217	
Birth weight (g)			N/A
Mean \pm SD	778 (SD N/A)	762 \pm 148	
Range	450-1000	345-1000	
Gestational age (weeks), mean \pm SD	26.5 (SD N/A)	26.5 \pm 2.3	N/A
Male sex, n (%)	122 (52.1)	112 (51.6)	.99
Multiple pregnancy, n (%)	71 (30.3)	68 (31.3)	.90
SGA, n (%)	98 (41.9)	63 (29.0)	.01
Use of antenatal steroid, n (%)	121 (51.7)	200 (92.2)	.0001
One-minute Apgar score \leq 3, n (%)	89 (38)	61 (28.1)	.03

Abbreviations: SD, standard deviation; SGA, small for gestational age; N/A, not available.

**Figure 1.** Survival curve of extremely low-birth-weight infants.**Table 2.** Comparison of Survival of Extremely Low-Birth-Weight Infants in 1993 to 2002 Versus 2008 to 2015 in Different Birth Weight Subgroups.

Birth Weight (g)	Survival on Discharge	Survival on Discharge	P
	1993-2002	2008-2015	
500 g or below	4/8 (50%)	3/7 (42.9%)	.78
501-750 g	46/87 (52.9%)	71/100 (71%)	.02
751-1000 g	117/139 (84.2%)	102/110 (92.7%)	.06
Overall	167/234 (71.4%)	176/217 (81.1%)	.02

birth weight $>$ 750 g (92.7%, 102/110 infants survived), and lowest in the group with the lowest birth weight of \leq 500 g (42.9%, 3/7 infants survived). Risk factors identified affecting survival using Cox regression analysis

included a lower birth weight, presence of severe IVH, and early-onset sepsis (all $P = .000$).

Comparison Between 1993-2002 and 2008-2015 Birth Cohorts. There was significantly higher overall survival rate in recent years (2008-2015) compared with that in 1993-2002 ($P = .02$; Table 2). When we categorized the survival according to birth weight, the improvement was most significant in the 501 to 750 g subgroup ($P = .02$).

Neonatal Morbidity

Major neonatal morbidities were shown in Table 3. A total of 85.3% (185/217 infants) were given surfactant for RDS, 63.1% (111/176 infants) were diagnosed to have chronic lung disease, and 29.5% (52/176 infants) were discharged home with oxygen. A total of 10.8% (19/176 infants) underwent patent ductus arteriosus ligation, 19.3% (34/176 infants) had severe ROP, 3.7% (8/217 infants) suffered from early-onset sepsis, 12% (26/217 infants) had severe IVH, and 7.8% (17/217 infants) had NEC (12/17 infants requiring surgery for NEC).

Comparison Between 1993-2002 and 2008-2015 Birth Cohorts. There was statistically significant increase in the use of surfactant replacement in RDS ($P = .0001$) and the use of home oxygen therapy on discharge ($P = .0001$) in the 2008 to 2015 period. The incidence of severe IVH and total number of NEC ($P = .01$ and $P = .0005$, respectively) were significantly decreased in the 2008 to 2015 cohort (Table 3).

Length of Stay (LOS) in Hospital and Duration of Invasive Mechanical Ventilation Among Survivors

Table 4 shows the LOS in hospital and duration of invasive mechanical ventilation among survivors. Mean LOS

Table 3. Comparison of Neonatal Morbidities in 1993-2002 Versus 2008-2015.

Neonatal Morbidity	1993-2002	2008-2015	P
Surfactant for RDS	155/234 (66.2%)	185/217 (85.3%)	.0001
Chronic lung disease	90/167 (53.9%)	111/176 (63.1%)	.11
Home oxygen	15/167 (9.0%)	52/176 (29.5%)	.0001
PDA ligation	14/167 (8.4%)	19/176 (10.8%)	.57
Severe ROP	33/167 (19.8%)	34/176 (19.3%)	.92
Early-onset sepsis	11/234 (4.7%)	8/217 (3.7%)	.76
Severe IVH	50/234 (21.4%)	26/217 (12.0%)	.01
NEC (total)	46/234 (19.7%)	17/217 (7.8%)	.0005
NEC (with surgery)	13/234 (5.6%)	12/217 (5.5%)	.99

Abbreviations: RDS, respiratory distress syndrome; PDA, patent ductus arteriosus; ROP, retinopathy of prematurity; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis.

Table 4. Length of Stay (LOS) and Duration of Invasive Ventilation Among Survivors.

	1993-1996	1997-2002	2008-2011	2012-2015	P
LOS (days)					
Mean \pm SD	112.25 \pm 32.0	108.53 \pm 41.0	96.3 \pm 30.0	96.0 \pm 34.8	.001
Range	49-438	51-338	43-219	54-218	
Duration of invasive ventilation (days)					
Mean \pm SD	26.7 \pm 21.0	16.7 \pm 18.2	9.8 \pm 11.5	9.2 \pm 14.6	<.0001
Range	0-80	0-84	0-55	0-71	

Abbreviation: SD, standard deviation.

in hospitals were 96.3 ± 30.0 days and 96.0 ± 34.8 days in the birth cohort of 2008 to 2011 and 2012 to 2015, respectively. Mean duration of invasive ventilation was 9.8 ± 11.5 days and 9.2 ± 14.6 days in the birth years of 2008 to 2011 and 2012 to 2015, respectively.

Among the survivors, there was a significant decrease in the mean LOS from 112.25 ± 32.0 days in the period of 1993 to 1996, 108.53 ± 41.0 days in 1997 to 2002, 96.3 ± 30.0 days in 2008 to 2011, to 96.0 ± 34.8 days in 2012 to 2015 ($P = .001$). Mean duration of invasive mechanical ventilation was shortened significantly from 26.7 ± 21.0 days (1993-1996), 16.7 ± 18.2 days (1997-2002), 9.8 ± 11.5 days (2008-2011), to 9.2 ± 14.6 days (2012-2015; $P < .0001$; Table 4).

Early Neurodevelopmental Outcomes and Growth of Survivors

One hundred forty-three out of 176 (81%) survivors were assessed at a corrected mean age of 18.1 ± 1.96 months (range = 8.6-28.5 months) for the birth year of 2008 to 2015. Table 5 shows the neurodevelopmental/behavioral and growth problems identified on follow-up. A total of 7.7% (11/143 infants) were diagnosed to have cognitive impairment with an overall DQ of <2 SD, and 11.9% (17/143 infants) required special

education service. A total of 4.2% (6/143 infants) had cerebral palsy, 2.1% (3/143 infants) with profound visual impairment, and 0.7% (1/143 infants) with profound hearing loss. A total of 12.6% (18/143 infants) were diagnosed to have autistic spectrum disorder, 7.7% (11/143 infants) with attention deficit hyperactivity disorder, and 2.1% (3/143 infants) with epilepsy. A total of 15.4% (22/143 infants), 13.3% (19/143 infants), and 11.2% (16/143 infants) having growth failure with body weight, head circumference, and body height $<$ third percentile, respectively.

Risk factors identified affecting cognition using univariate logistic regression analysis included male sex ($P = .003$), earlier birth years ($P = .013$), and longer duration of invasive ventilation ($P = .000$). Risk factors identified affecting behavior (autistic spectrum disorder or attention deficit hyperactivity disorder) and growth using univariate logistic regression analysis included male sex ($P = .015$) and lower birth weight ($P = .038$), respectively. No significant risk factors could be identified for cerebral palsy, and hearing and visual impairment. Table 6 shows the result of multiple logistic regression analysis.

Comparison Between 1993-2002 and 2008-2015 Birth Cohorts. There were significantly lower rates of cerebral

Table 5. Neurodevelopmental Outcomes and Growth at Corrected Age of 18 to 24 Months.

	1993-2002	2008-2015	P
Survivors	167	176	
Developmental assessment performed	126	143	
Developmental quotient (overall <2 SD)	21 (16.7%)	11 (7.7%)	.04
Locomotor	20 (15.9%)	11 (7.7%)	.06
Personal-social	20 (15.9%)	8 (5.6%)	.01
Hearing and speech	12 (9.5%)	32 (22.4%)	.01
Coordination	14 (11.1%)	13 (9.1%)	.73
Performance	11 (8.7%)	9 (6.3%)	.60
Cerebral palsy	17 (13.5%)	6 (4.2%)	.01
Profound visual impairment	13 (10.3%)	3 (2.1%)	.01
Profound hearing loss	6 (4.8%)	1 (0.7%)	.09
Autistic spectrum disorder	N/A	18 (12.6%)	N/A
Attention deficit hyperactivity disorder	N/A	11 (7.7%)	N/A
Need for special education service	24 (19.0%)	17 (11.9%)	.14
Epilepsy	1 (0.79%)	3 (2.1%)	.71
Growth failure (<3%)	N/A		N/A
Body weight		22 (15.4%)	
Head circumference		19 (13.3%)	
Body height		16 (11.2%)	

Abbreviations: SD, standard deviation; N/A, not available.

Table 6. Results of Multiple Logistic Regression With Cognitive Impairment and Growth Failure as Outcome Variables.

	Cognitive Impairment		Growth Failure	
	Odds Ratio (95% CI)	P	Odds Ratio (95% CI)	P
Sex (male)	7.29 (1.83-29.02)	.005	NS	
Birth years (recent years)	0.66 (0.50-0.88)	.005	NS	
Duration of invasive ventilation (longer)	1.07 (1.03-1.11)	.000	NS	
Birth weight (heavier)	NS		0.99 (0.987-0.995)	.000
Gestational age (more mature)	NS		1.52 (1.22-1.89)	.00

Abbreviations: CI, confidence interval; NS, no significant association in univariate analysis.

palsy ($P = .01$) and visual impairment ($P = .01$) in the 2008 to 2015 cohort (Table 5). Rate of significant developmental delay defined as an overall DQ of <2 SD as well as the rate of significant delay in the personal-social subscale were significantly lower in the recent cohort (2018-2015) compared with 1993 to 2002 ($P = .04$ and $P = .01$, respectively). However, delay in the hearing and speech subscale was significantly higher in the recent cohort ($P = .01$). The need for special education service, rate of profound hearing loss, and epilepsy had remained similar over the years.

Discussion

With advances in obstetric and neonatal care, the survival of ELBW infants has improved dramatically over the past few decades.⁶ Our results compared favorably

with other international data,² with a significant improvement in the overall survival for ELBW infants from 71.4% (1993-2002) to 81.1% (2008-2015), especially in the group with a birth weight of 501 to 750 g. The improvement in perinatal care was supported by a decrease in babies born SGA, increased use of antenatal steroid, more babies born with an Apgar score of >3 at 1 minute of life, increased use of surfactant therapy, and decreased incidence of severe IVH and NEC.

Among survivors of ELBW in our study, infants were able to be discharged from the hospital earlier, with the mean LOS reduced from 112.25 days to 96.0 days (from 1993-1996 to 2012-2015). This may be attributed by the reduction in the duration of invasive ventilation (from 26.7 days to 9.2 days) and more babies being discharged with home oxygen therapy (from 9% to 29.5%) with time. Shortening of hospital stay also

carries an important economy impact with cost savings, reducing burden on the health care system.

Previous studies of neurodevelopmental outcomes among extremely premature infants have shown variable results, with reports of increased,^{7,8} unchanged,⁹⁻¹¹ or decreased rates of neurodevelopmental impairment over time.^{12,13} In our study, neurodevelopmental outcome at the corrected age of 18 to 24 months has been shown to be better in the past 2 decades. The prevalence of cerebral palsy decreased from 13.5% to 4.2% from 1993-2002 to 2008-2015 birth years. This phenomenon could be partly explained by the decreased incidence of severe IVH. Cerebral palsy rate in our recent cohort compared favorably with international data (8.5% in Vermont Oxford Network²).

In our study, the proportion of infants with significant developmental delay (with overall DQ of <2 SD) or significant delay in the personal-social aspects declined significantly from 16.7% to 7.7% and 15.9% to 5.6%, respectively, from birth years 1993-2002 to 2008-2015. Improvement in cognitive outcome could be explained by a reduction in the duration of invasive ventilation, as a longer period of invasive ventilation is found to be a risk factor for cognitive impairment in our study. In recent years, our unit has been managing RDS more with continuous positive airway pressure support with subsequent selective surfactant administration, that is, INSURE (INtubation, SURfactant administration, then Extubation), therefore avoiding unnecessary or prolonged invasive ventilation. However, significantly more infants were having speech delay in recent cohort (22.4% in 2008-2015) compared with 9.5% in 1993 to 2002. This finding is consistent with a recent meta-analysis showing a higher prevalence of autistic spectrum disorder in the preterm population,¹⁴ resulting in impairment in the speech development.

Although the rate of severe ROP has not changed, the rate of visual impairment has declined significantly from 10.3% to 2.1% (from 1993-2002 to 2008-2015). This may have been contributed by the regular surveillance program for ROP in ELBW babies, with early identification of high-risk group and provision of timely intervention for severe ROP, minimizing the risk of visual impairment in the long-term. However, comparing with another recent cohort in the United States,³ with the rate of profound visual impairment of <1%, there is room for improvement in our center, for example, stringent titration of oxygen to achieve target saturation to prevent oxygen toxicity.

One limitation of our study is that we only reported on the neurodevelopmental outcome at 18 to 24 months corrected age. Subtle neurocognitive impairment and specific learning disability may not be detected at this

early age and longer term follow-up is required. Future directions should include early identification of at-risk children using parental questionnaires, followed by longer term follow-up with standardized evaluation by formal psychometric tests.

In conclusion, we showed an improvement in survival and short-term neurodevelopmental outcome between the birth cohorts of 1993 to 2002 and 2008 to 2015, as a result of an improvement in the perinatal care of these infants over all these years.

Author Contributions

YYC: Contributed to conception and design; drafted manuscript.

MSCW: Agrees to be accountable for all aspects of work ensuring integrity and accuracy.

RMSW: Contributed to conception and design; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

WWYT: Critically revised manuscript.

WHSW: Contributed to design; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

SLL: Contributed to conception and design; critically revised manuscript; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of Conflicting Interests

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